Application of Statistical and Decision-Analytic Models for Evidence Synthesis for Decision-Making in Public Health and the Healthcare Sector

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Abstract

With the awareness that healthcare is a limited resource, decision-makers are challenged to allocate it rationally and efficiently. Health economic methods of evidence synthesis for decision-making are useful to quantify healthcare resource utilisation, critically evaluate different interventions and ensure the implementation of the most effective or cost-effective strategy. The nine studies included in the present cumulative doctoral thesis aim to demonstrate the capability of statistical and decision-analytic modelling techniques to inform and support rational healthcare decision-making in Germany. Five studies apply statistical modelling in analyses of public health and health economic data. They show that the developed models are valuable instruments for examining patterns in the data and generating knowledge from observable data which can further be used in devising disease management and care programs as well as economic evaluations.

Further, two health economic evaluations, which adopt the decision-analytic-modelling approach, show that decision-analytic modelling is a powerful tool to represent the epidemiology of infectious and non-infectious diseases on a population level, quantify the burden of the diseases, generalise the outcomes of clinical trials, and predict how the interventions can change the impact of the diseases on the health of the population. Additionally, two literature reviews examine the application of decision-analytic modelling in health economic evaluations. The first study reviews and empirically analyses health technology assessments by the German Institute for Medical Documentation and Information and demonstrates that the application of decision-analytic models improves the evidence produced for policy-making in the healthcare sector in Germany. The second systematic review focuses on methodological choices made in constructing decision-analytic models and explains how critically the structural and parametrical assumptions can influence the final message of the economic evaluations and shows that building a validated, reliable model as well as the transparent reporting is of high priority in facilitating the communication and implementation of the most cost-effective course of action.

Overall, the present thesis shows the relevance and advantage of the application of models in synthesising evidence for decision-making. The included studies contribute to the current and future development of the methods used to address the problems of health economic efficiency. Further advances in the computational modelling techniques and data collection, from one side, will ease the decision-making process, but, from another side, will require increasing competence and understanding within the decision-making bodies.

Keywords

Evidence synthesis, decision-making, health economic evaluation, healthcare data, public health data, statistical modelling, decision-analytic modelling, vaccination, screening.

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CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
cART	Combined antiretroviral therapy
CDC	The Centers for Disease Control and Prevention
CORSAR	Cost and Resource Utilization Study in Antiretroviral Therapy
CT	Computed tomography
DAM	Decision-analytic model
DIMDI	The German Institute of Medical Documentation and Information
EAPY	Efficacy-adjusted protection years
EQ-5D-3L	EuroQol five dimensions three levels
EVIDEM	Evidence and Value: Impact on DEcisionMaking
EVPOT	Expected vaccine protection over time
GLM	Generalised linear model
HTA	Health technology assessment
IQWiG	The Institute for Quality and Efficiency in Healthcare
JIA	Juvenile idiopathic arthritis
LYG	Life year gained
NELSON	The Netherlands-Leuvens Screening Trial
NLST	The National Lung Screening Trial
NMP	Nodule management protocol
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PCV13	13-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RKI	Robert Koch-Institute
STIKO	Standing Vaccination Committee at the German Robert-Koch Institute
TTO	Time trade-off
VAS	Visual analogue scale
WTP	Willingness to pay
WTU	Willingness to use

1. Introduction

Healthcare is a highly complex, dynamic and diverse economic sector which functions within conditions of numerous uncertainties, individual preferences and technological progress. This environment creates a constant challenge for decision-makers to reconcile the increasing costs and the growing demand with limited resources and funds. The rational allocation of scarce healthcare resources requires evidence-based decision-making (1). Evidence can be primarily obtained through observation and data collection (2), however, the production of knowledge needs the process of synthesis. Modelling techniques facilitate the synthesis of evidence, which cannot be directly observed, and serve as decision-supporting tools in economic efficiency problems (3). They become increasingly important in the health economic methodology and are frequently emphasised in questions of healthcare resource allocation.

Two modelling approaches are the focus of the present work: statistical and decision-analytic modelling.

Synthesising evidence using statistical modelling is achieved via the application of statistical models directly to the observed public health and economic data. It comprises of the examination of patterns in the data as well as the investigation, explanation, and prediction of relationships between the observed variables (4). A wide variety of statistical models has been developed for the analysis of public health and health economic data, making it challenging to choose the right modelling approach for the problem at hand (5). This choice should be guided by the structure of the data and hypotheses about the relationships between the variables (4). The latter is driven by the existing knowledge, and the former requires the analysis of the statistical distributions of the included variables.

Synthesising evidence using a decision-analytic model includes the integration of the observed data from different sources into one system within a health economic evaluation (6). Health economic evaluations are performed to assess the costs and consequences of preventive and therapeutic interventions, estimate maximal or threshold values of important characteristics (e.g. a break-even price), and optimise strategic parameters (e.g. age-range and time of administration). A health economic evaluation comprises of a set of comparative methodologies that weigh the costs of a strategy against its benefits or consequences. The most frequently used forms of health economic evaluations are cost-utility analysis, cost-effectiveness analysis and cost-benefit analysis (7).

The assessment of randomised controlled trials (RCT) and decision-analytic modelling are the two main vehicles for a health economic evaluation providing evidence for the comparison of alternative courses of action (7). Although RCTs are a good source of

estimates of health outcomes, effects, and resource utilisation, they do have limitations. RCTs tend to report evidence specific to their particular setting for a group of patients and can contain a possible bias due to participant selection (8). Also, RCTs are not suitable to provide estimates on the population level and might be of duration too short to capture all relevant long-term outcomes (7). Moreover, even well designed and conducted RCTs can provide evidence only on a few options of one intervention but cannot facilitate the inclusion of multiple varying alternatives. In addition, RCTs often report relevant clinical data but do not provide the evidence necessary for an economic evaluation such as impairment of quality of life and/or resource utilisation.

A decision-analytic model (DAM) uses input data from different sources, projects outcomes of alternative decisions and produces information on costs and benefits of a healthcare intervention. Decision-analytic modelling proves to be useful if there is a need to generalise the outcomes of RCTs to other settings and population groups, combine evidence from a range of sources, and extrapolate their impacts beyond the time horizon of the respective RCTs (7). In addition, decision-analytic modelling facilitates detailed comparisons of alternatives where trials do not exist.

Frequently, the term “decision-analytic model” represents an economic analysis based on a decision-tree (6). Therefore, for the purpose of this work the term “mechanistic model” will be used to denote more complex mathematical formulations, which are used to simulate a natural process, such as a dynamic-transmission model or a microsimulation model while the term “decision-analytic model” will be reserved for describing a complete computation of evidence needed for a decision-analysis which includes a mechanistic model and an economic evaluation conducted on its basis. The design of a mechanistic model (9) is based on what is known about the process that it is intended to reproduce and includes the states of the natural course of events (e.g. disease, infection, exposure, etc.), transition principles, and time. Depending on the model type, the output values of a mechanistic model illustrate trajectories of either an individual or a population entered into the modelled system. Aggregations of the returned output values are consequently used in health economic comparative analyses.

The increasing complexity of the decision-analytic methodology has raised the need to establish guidelines for a good practice of model development which have been published in increasing numbers (10–15). In this work, the following generalised framework is suggested to broadly describe the general approach of the application of decision-analytic models in health economic studies.

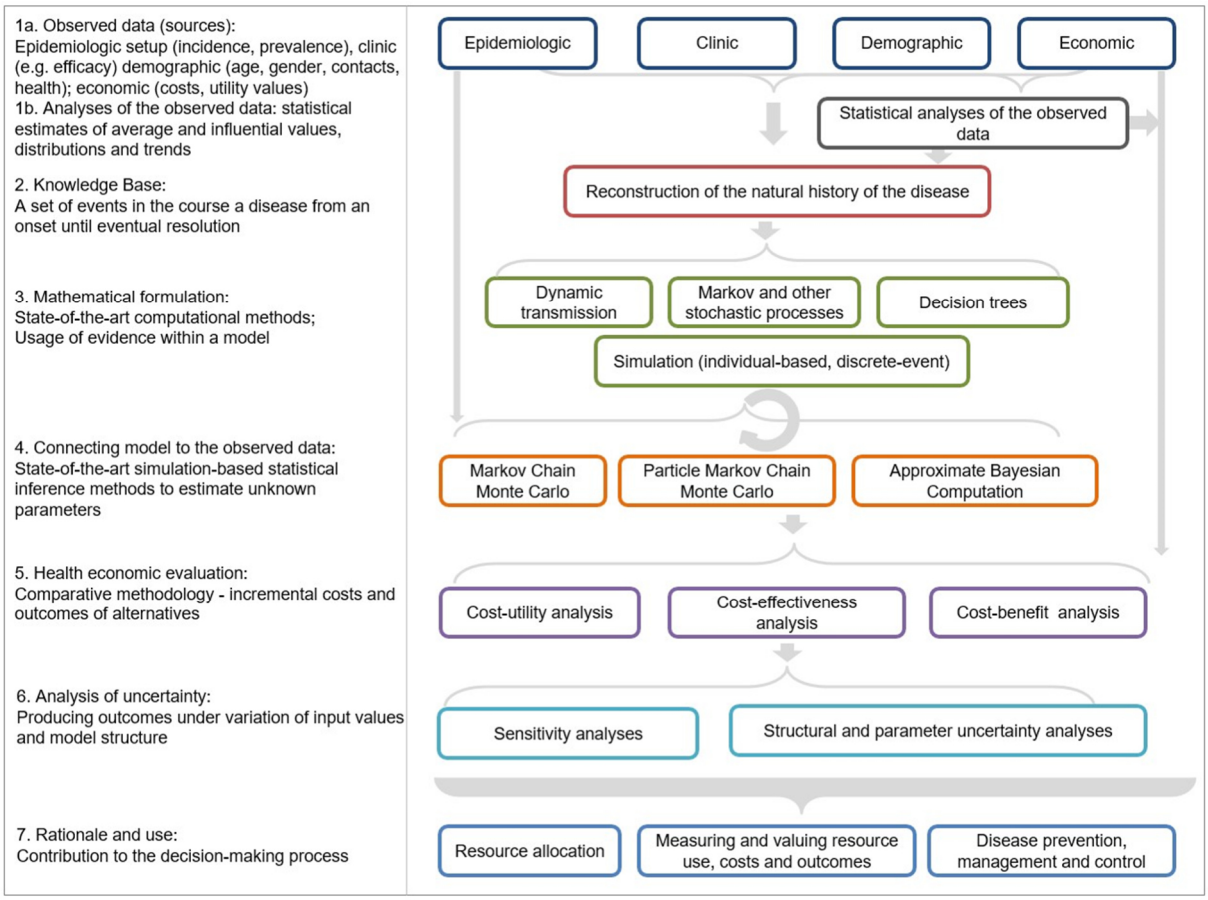

Figure 1: Framework for the application of decision-analytic modelling to synthesise evidence for decision-making.
Source: own representation based on (7, 10–15).

This framework can be understood as follows:

1) *Obtaining the observed data on the topic of study.* The list of sources of data used for health economic evaluations includes, but is not limited to, epidemiological observational studies, clinical trials, observational cohort studies, socio-economic population statistics, costs, and quality of life data. The information provided in the wide range of data from different sources is combined in a systematic approach using a decision-analytic model. This can be seen as being composed of two parts: a mechanistic model and an economic appraisal which is informed with the output values of the mechanistic model and the economic data.
2) *Researching the knowledge base.* The development of a mechanistic model begins with a reconstruction of a sequence of events and pathways which represent the natural course of the studied health condition. If there is sufficient information about its biological and epidemiological features, the course of events and governing transition principles can be known and sketched. Although the knowledge base of many health conditions is large, there might not be sufficient data to model the natural process down

to the smallest detail. Thus one natural process can be reconstructed using different models with one being the closest to reality.

3) *Writing and programming a mathematical formulation.* The sketched model structure is converted into a mathematical formulation using, for example, the theory of differential equations, mathematical equations with stochastic assumptions, survival analysis, and/or other approaches.
4) *Parameterising the model.* The models are parameterised with input values that are obtained using the available evidence; however, often, not all governing parameters can be observed. For example, mathematical models based on differential equations have been proven to be a powerful tool in understanding dynamic behaviour such as the epidemiology of infectious diseases and predicting their impact on the population (16). However, in infectious diseases, often only a part of the reality is observed. As examples might serve a) the proportion of the ill people who seek healthcare or become hospitalised as compared to all the people infected or b) the time of symptoms onset but not of the transmission of the pathogen. Therefore, the problem of model parameterisation is twofold: from one side, it depends on the model chosen to reproduce the reality and, from another side, the connection of this reproduction to the observed data. The connection of the model to the data is conducted through a process of fitting, i.e. a process of parameterisation of the model to induce it to return output values which are close to those observed in reality (17). Commonly used techniques comprise of simulation-based inference which combines mechanistic and statistical approaches. They are based on calculations of probabilities that, given a particular vector of inputs, the observed data are the model output. The estimated parameters are further used to inform the model to predict the outputs over a time horizon which cannot be observed.
5) *Conducting health economic evaluation.* The constructed mechanistic model can be used either to investigate the natural course of a disease or, of more importance, to simulate the effects of a preventive or therapeutic intervention. The model output values for each strategy inform the succeeding economic analysis, which also has to be adequately conceptualised to correctly address the decision problem. It requires a detailed consideration of intervention settings, perspectives, time horizons, discounting rates, representative costs, and health outcomes.
6) *Analysing uncertainty.* The exploration of uncertainty and a critical overview of the results is the next key component of decision-analytic modelling (10, 15). Uncertainty comes from multiple sources such as demographic and epidemiologic uncertainties, the observational process, the data collection, parameter estimation procedures, and incorrect structural assumptions in the model design.

7) *Informing decision-making.* The evidence synthesised using a decision-analytic modelling study is used to convey a message about the most effective and cost-effective alternatives to allow for rational decision-making.

It is important to note that in the field of decision-analytic modelling, it is impossible to come up with a “one size fits all” methodology. It is, therefore, up to the researcher to address the nature of the disease, the intervention, and the available data to determine which method to use. Due to the likely complexity of the models, it is important to thoroughly review the assumptions made and the evidence used in the development of the model before deciding whether the results of this model are credible and valid for the decision at hand. Decision-makers need to “trust” the model and be able to screen out those of low predictive quality to foresee the true potential health and economic impacts of different strategies as well as select programs that maximise the effects of the invested healthcare resources. A fundamental problem for a judgment about the validity of a decision-analytic model is to see whether the model adequately represents the epidemiological and economical setup behind the envisioned intervention and provides the best possible evidence given the available data. In other words, is the model fit for the stated purpose or rather misleading? This concerns both the mechanistic model, which represents the epidemiology of the studied disease as well as the economic appraisal. Although there are multiple instruments and checklists, which can be used to assess the quality of economic evaluations (18), only a few of them include critical considerations of the assumptions and the methods used in the modelling studies. Therefore, a systematic examination and transparent reporting of the parametric and structural uncertainty is a requirement for a decision-model-based health economic study of good quality and value for decision-makers.

The present cumulative doctoral thesis focuses on the evidence synthesis for decision-making in public health and the healthcare sector via collecting data, conducting extensive statistical analyses, and building complex decision-analytic models. The overall framework is shown in Figure 2. Primary evidence is obtained via observations, experiments and data collections from first-hand sources (19). Statistical models are applied to synthesise knowledge from the primary data for policy-making (Articles 1 to 5). Decision-analytic models are applied to integrate the primary data from various sources in order to produce new data needed for comparing and evaluating different public health strategies (Articles 6 to 9). The thesis includes two economic evaluations where both statistical and decision-analytic modelling approaches are applied in one analysis. This includes using the outcomes of statistical models as input values for a decision-analytic model and probabilistic analyses of uncertainty, incorporating the estimated statistical distributions and regression models in a mechanistic model as structural elements, as well as applying the methods of simulation-based inference to connect a mechanistic model to the observed data through a process of

fitting. Additionally, these multiple possible interconnections are demonstrated throughout the present text to point out that the application of both statistical and decision-analytic approaches in one decision-analytic modelling study increases the ability of the model to approximate reality and provide evidence with less uncertainty.

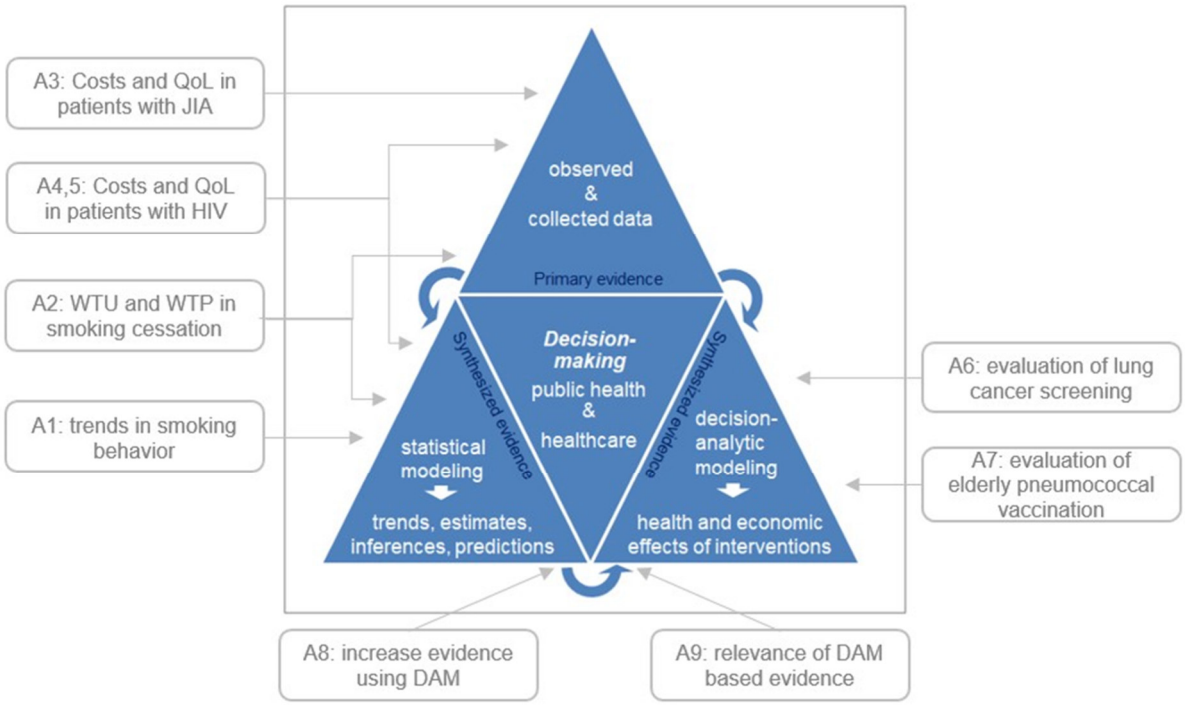

Figure 2: Integrated framework of evidence synthesis using statistical and decision-analytic modelling and contribution of the included studies.
JIA - juvenile idiopathic arthritis; DAM - decision-analytic modelling, A - Article; WTP - willingness to pay; WTU - willingness to use.
Source: own representation.

This text describes the nine included studies and is structured along with the following central research questions:

1. *What is the contribution of statistical models in the synthesis of evidence for health economic evaluations and decision-making in public health and the healthcare sector?*
2. *What are the capabilities of decision-analytic modelling to synthesise evidence about complex public health interventions?*
3. *Does decision-analytic modelling as an instrument of health economic evaluations advance evidence synthesis for rational decision-making in public health and the healthcare sector?*

The text begins with the description of data collection and the application of statistical models in order to investigate and analyse the patterns in the observed public health and health economic data in Germany as well as to synthesise evidence for policy-making. The section presents the usage of two regression methods that are applied in the analysis and prediction

of, firstly, health-related behaviour and, secondly, estimations and investigations of costs and health-related quality of life (Section A: articles 1 to 5).

The text continues with a discussion of the usage of decision-analytic models built on complex mechanistic models. It demonstrates how these modelling techniques can facilitate decision-making on complex healthcare interventions (Section B: articles 6 and 7). The section presents two health economic evaluations which are conducted to address decision problems for two large-scale public health interventions: screening and prevention. Due to their nature, these two interventions require different approaches in the development of the corresponding mechanistic model to facilitate an economic evaluation of their payoffs. A decision problem on preventive measures includes a population without the disease of interest and intervention, which aims at reducing the risk of acquiring this disease (6). Screening, in turn, affects individuals at a high and average risk of developing the disease or those who have developed the disease but present no symptoms. Screening, therefore, aims at the detection of the underlying disease at an earlier and more treatable stage (6). The particularities of the decision-problem at hand, the development of decision-models as well as the application of statistical models to inform the mechanistic models and the economic analyses are described and discussed.

Further, two reviews address the application of decision-analytic modelling as an instrument of health economic evaluations (Section C: articles 8 and 9). The first review and empirical analysis of health technology assessments of the German Institute for Medical Documentation and Information demonstrates the advantages of using decision-analytic models in producing evidence for policy-making in the healthcare sector in Germany. The second publication is a comprehensive systematic review of economic evaluations addressing the issues of transparent reporting, choices of assumptions and methods in conducting decision-analytic modelling thereby showing their impact on the validity of the models and the evidence synthesis for decision-making.

Finally, the third chapter summarises the contribution of the nine articles, describes the general limitations of this work and gives an outlook on further research needs in the field.

2. Contribution of the present cumulative doctoral thesis

A. Synthesising evidence using health economic and public health data: contribution of statistical modelling

(1) Analyses of data on health-related behaviour (articles 1 and 2)

The examination of health-related behaviour is of high importance in public health because major behavioural risk factors, such as smoking, obesity, and alcohol consumption, are proved to adversely affect health outcomes and induce consumption of healthcare resources (20, 21). Two papers of this thesis address smoking behaviour from different perspectives.

In the first study, “Estimation of age -, gender - and birth cohort-specific parameters of smoking behaviour for the German population” (Article 1), we use statistical modelling to establish time-dependent patterns of smoking behaviour of multiple German birth cohorts. We perform comprehensive analyses of smoking history trends in Germany for birth cohorts from 1920 to 1980 and obtain summaries of their lifetime smoking which contribute to our understanding of the adverse impacts smoking might have on the health of the population. We also project these estimates forward to the year 2025, aiming to instigate further research in this field. The statistical models are determined after examining the dataset obtained from three cross-sectional surveys conducted by the Robert Koch-Institute (RKI) between 1997 and 2012. They provide a large pooled sample size of 77,882 respondents and contain all variables of interest for our analyses: smoking status at the interview date, age at starting and quitting smoking, the form of smoking, and the number of cigarettes smoked per day. To find and explore the patterns in these data we use logistic age-cohort models to estimate conditional probabilities and apply thin plate regression splines, a technique for data interpolation and smoothing (22), within the logistic models due to nonlinearity of the relationships between the variables. Similar models are used in the analysis of surveys conducted in the USA (23). However, the consumption of cigarettes varies throughout the world, and our representation of the experience in Germany provides a valuable addition to our understanding of the smoking trends.

The results of this study include estimates of smoking initiation probability, smoking cessation probability, current and former smokers’ prevalence and smoking intensity. For instance, the highest probability of starting smoking is estimated to be between the age of 16 and 18. Also, women in their 20ies and the elderly 60 to 65 years old have a higher probability of quitting smoking. Additionally, both men and women achieve the highest smoking intensity between 40 and 45 years of age. The graphical representations of the estimates provide an opportunity to explore the prevalence of active smoking and quit smoking as well as probabilities of smoking initiation and cessation over time.

It is important to note, that the use of cross-sectional surveys in order to obtain longitudinal estimates such as the prevalence can be challenging. In our study, the estimation of the smoking trends in the early cohorts, which were only included in the survey at a higher age brings a critical bias. For example, in the case of the 1920 birth cohort, the participants were 77 years old when the earliest survey was conducted in 1997. The bias is in favour of the participants that never smoked due to their likelier survival until 1997. The smokers of the 1920 birth cohort had likely died because of the adverse health effects of cigarette smoking or other causes before the survey took place. Despite this limitation of our study, the projections for the recent birth cohorts comprise valuable inputs to studies of smoking trends. For instance, from the data created in this study researchers can estimate accumulated exposure to cigarette smoking and the risk of smoking-related diseases of people in Germany. As it is further described, the obtained gender-, birth cohort- and age-specific estimates of the probabilities of smoking initiation and cessation are applied as input values into a microsimulation model in order to predict future smoking behaviour of the modelled population and adjust the computation of individual probabilities of onset of lung cancer in a study which is dedicated to the economic evaluation of lung cancer prevention using lung screening with a computed tomography (CT) scan (Article 6).

In the second study, “Analysis of driving factors of willingness to use and willingness to pay for existing pharmacological smoking cessation aids among young and middle-aged adults in Germany” (Article 2), we address smoking cessation as a target of a possible public health campaign. The main aim of the study is to collect data on willingness to use (WTU) and willingness to pay (WTP) for pharmacological aids to quit smoking. WTU and WTP are recorded as yes/no answers. Additionally, WTP is quantified using a contingent valuation method with payment cards (24) and categorised into 10-Euro intervals. The collected data are further statistically analysed to provide inference on the main drivers of the maximum price a current smoker would accept to pay. The odds ratios of WTP and WTU are estimated using logistic regressions which are the most popular models for dichotomous dependent variables such as yes/no records of WTU and WTP. The predictors are chosen based on the hypothesised relationships between the outcome variables and a set of characteristics that describe the socio-economic status of the respondents, their smoking habits, and their environment. We use another technique to analyse the dependent variable WTP, which is given as an interval variable. WTP bids are regressed against the same set of predictors using an accelerated failure-time model (25). Although being an unconventional technique to be applied for WTP, it allows the calculation of odds ratios in terms of WTP of a higher or a lower value using the intervals as the dependent variable (26). The model is informed with a Weibull distribution which gives the best approximation of the upper and lower values of the WTP bids. The study shows that WTP for the pharmaceutical aids is mainly driven by the

addiction level; however, the average measure of WTP is still below the market price for all therapeutic options. The findings of this study suggest that when aiming to reduce smoking exposure by means of pharmacological smoking cessation aids, policy developers should consider targeting the smokers with a higher addiction level and include measures which would decrease out-of-pocket payments, i.e. by lowering the effective price. The sample, however, is limited to young and middle-aged people and is not representative of the total German population. Further investigations in this direction would benefit from a larger and more heterogeneous sample of smoking individuals and a more thorough questionnaire which allows the exploration of non-monetary incentives for quitting smoking. Although it has not been done yet, the results of the study might be applied in a decision-analytic model as a preventive comparator to an intervention such as a lung screening program, that is, as another public health intervention that would target the reduction of exposure to the carcinogenic agents rather than the detection of lung cancer in an early stage.

(2) Analyses of data on healthcare costs and health-related quality of life (articles 3 to 5)

(2.1) Measuring healthcare utilisation, costs and health-related quality of life

Cost data are commonly obtained by multiplying appropriate costs per unit by the quantities of healthcare resources utilised. The costing data used in economic evaluations frequently come from administrative databases collected by hospitals, statistics offices, and insurance companies (27). Alternatively, self-reported questionnaires present an opportunity to capture data on the patient costs and resource utilisation such as out-of-pocket expenditures, caregiver time, travel time and costs, as well as waiting time (28). These inputs are valuable when representing the cost side of disease and considering what intervention could save, from the societal perspective.

Both methods of data collection have their advantages and disadvantages. The administrative data allow for a sufficient sample size needed to obtain representative estimates, but do not include complete direct and indirect patient costs and spent resources. The data collected using self-reported questionnaires might be of small sample size, unobtainable in a timely manner, and at risk of biases and distortions due to, for example, inaccurate recalls, sample selections, and survey processes (28). This might as well bring bias into an economic evaluation and impact the validity of the obtained conclusions. A survey using questionnaires for the evaluation of resource utilisation is often accompanied by other questionnaires for measuring health-related quality of life which is quantified either with a generic preference-based instrument such as EQ-5D (EuroQol five dimensions) or with as a disease-specific instrument. The former instruments are commonly used in health economic evaluations which use quality-adjusted life-years (QALYs) as health outcomes.

In this thesis, three studies illustrate analyses of data collected with the goal to capture costs and quality of life of patients using self-reported questionnaires:

The study “Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe” (Article 3) reports the data collected from patients with juvenile idiopathic arthritis (JIA) from several countries of Europe. The survey captures data on resource utilisation by and outcomes for the patients and caregivers, providing an insight into additional societal losses due to JIA. The study demonstrates a considerable increase in annual healthcare costs for JIA patients compared to other published studies. The reasons for these estimates are the inclusion of costs of non-professional caregivers, usage of biologics, and longer hospital stays. The study also measures the impairment of quality of life of the patients as well as the caregivers, showing that the costs and outcomes of non-professional caregivers should be included in economic evaluations of interventions against JIA. Due to a low response rate, the collected dataset is of small size (total of 161 patients) and shows heteroscedasticity of the age variable. Therefore, no regression is applied. Economic evaluations, however, require a range of valid cost estimates across population groups and in order to produce more informative analyses a larger and a more representative sample would be necessary.

(2.2) Statistical analyses of healthcare costs and health-related quality of life

The following two studies examine a dataset obtained during a 96-week longitudinal survey of people living with HIV in Germany: “Cost and Resource Utilization Study in Antiretroviral Therapy (CORSAR)”. Data were collected in eight healthcare providers and present a sample of 1154 HIV-infected individuals in Germany which is considered to be a representative sample (around 2% of people living with HIV and AIDS in Germany). Demographic, clinical, and medication data were obtained using a standardised patient questionnaire.

In the paper “Analysis of contemporary HIV/AIDS health care costs in Germany: driving factors and distribution across antiretroviral therapy lines” (Article 4) we analyse observed costs and resource usage attributable to an HIV infection. For this analysis, resource utilisation and healthcare expenditures are summarised into annual total costs calculated with a bottom-up approach. The total costs include both direct (medical and non-medical) and indirect costs for the selected patients with HIV. All costs are calculated based on price information obtained from publicly-available databases. Annual total costs in the resulting dataset are modelled as the dependent variable. The aim of this study is to investigate relationships between the mean annual total costs and the characteristics of the patients with a positive HIV diagnosis. An initial investigation of the distribution of the costs data shows that they are characterised by skewness and a heavy right tail. This is often observed when

examining costs and resource usage in healthcare (29). Other characteristic difficulties of cost data are multimodality, missing observations, outliers, and excess zeros.

The following classes of estimators are employed in the publication: a linear regression using log-transformation of the cost data and generalised linear models (GLM) with logarithmic link functions. These include models common to the medical and econometric literature. GLMs are convenient for statistical analyses of cost data in healthcare due to the possibility of linking non-normal dependent variables to linear combinations of independent characteristics (29). In a generalised linear model, predictors are combined additively as in the linear models, and the properties of the response variable are characterised by the particular distribution (mostly from the exponential family of distributions). Additionally, the variance is a function of the mean, and the link function determines the appropriate scale (30). In the study, two generalised linear models are compared, each with a logarithmic link function and with conditional distributions that are inverse Gaussian and gamma. The inverse Gaussian is applied to report the results because it provides a better fit and approximation of the CORSAR cost data.

The added benefit of the application of GLMs with logarithmic link functions is that the estimates of the coefficients are interpretable as the logarithm of a relative change in the mean cost associated with a one-unit change in the predictor variable. Therefore, using the estimates of the regression coefficients and the covariance matrix we can describe the relationship between the costs and the patient characteristics in terms of relative cost ratios, i.e. how the annual costs would change relative to the mean costs of the reference patient when one or more patient characteristic is varied. The obtained cost ratios can also be transferred to other populations with reasonably similar socio-demographic settings.

The study, however, could provide more information if the survey included questions about the path of the HIV-transmission and the patients who have not received combined antiretroviral therapy (cART). Despite some limitations, the study shows possible ways to optimise the costs of HIV-care and clinical practice. For example, the prescription of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens can result in lower total costs compared to the standard protease inhibitor regimens. Also, management aiming to improve adherence and further development of cART regimens with enhanced forgiveness (meaning the ability of antiretroviral therapy to sustain viral suppression, despite insufficient adherence) have a potential to prevent part of the high-cost cases of HIV treatment. These measures should be seen as necessary elements of strategies in the management of HIV infections.

In the subsequent study “Estimation of utility values and factors driving health-related quality of life in people living with HIV and AIDS and receiving cART in Germany: analysis of a

cohort study" (Article 5), we analyse data collected on the quality of life of the participants in the CORSAR survey. Health utilities are measured using the generic preference-based instrument, EQ-5D-3L, and therefore can be applied in calculations of the health outcomes in health economic evaluations of interventions targeting HIV management and prevention. Health utilities are valuated using time trade-off (TTO) method and quality of life with the visual analogue scale (EQ-VAS). We provide a comprehensive descriptive analysis so that the reported health utilities estimated across varying HIV-related health states (CD4-T cell count, CDC (The Centers for Disease Control and Prevention) classification, comorbidity, etc.) as well as demographic and therapeutic (treatment regimen) characteristics can be applied in further research.

Additionally, we perform a regression analysis seeking to identify factors that are associated with the quality of life of people living with HIV and AIDS in Germany. The utility values, by definition, are bound between 0 and 1. Therefore, the chosen regression model has to perform well in terms of bias and precision, given the bounded nature of the dependent variable. A generalised linear model is chosen to regress the utility outcomes against patient characteristics with the application of a three-parameter beta-inflated distribution for the TTO values and a four-parameter beta-inflated distribution for the EQ-VAS values (31). The beta distribution is a common choice to approximate the values in a range of 0 to 1 and is often applied in the analysis of health utilities in health economics (7). The independent predictors are chosen based on the previously published review of major factors influencing the quality of life of people living with HIV and AIDS (32). As results, we obtain an explanatory model of the health-related quality of life and measure the relationships between the utility values and a wide set of patient characteristics. The overall results present a quantification of the quality of life impairment and can be applied as such in further studies in the field. The main limitation of this study is the application of the single EQ-3D-5L instrument without complementing it with an HIV-specific instrument. It is, however, somewhat inconvenient for the participants of a survey with self-reported questionnaires to fill out multiple forms. The main contribution of this study is the representative estimates of utility values over multiple health states for people living with HIV and AIDS in Germany.

With the development of strategies to manage an HIV-infection as a chronic condition and with the ongoing search for therapeutic agents and vaccines, the results of both studies provide valuable input parameters for costs and health outcomes in health economic evaluations. Additionally, the estimated distributions will facilitate probabilistic sensitivity analyses. For example, this work is being continued with an ongoing study which conducts a health economic evaluation based on a dynamic-transmission model of HIV pre-exposure prophylaxis strategies for men who have sex with men.

B. Synthesising evidence about complex public health interventions: contribution of decision-analytic models

(1) Application of decision-analytic modelling in the evaluation of a screening intervention (article 6)

The study entitled “Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting” (Article 6) examines probable outcomes of the introduction of a screening program for non-small cell lung cancer in Germany. Questions such as “What are possible screening strategies?”, “What are the payoffs of the alternative screening strategies?”, and “What is the most effective and cost-effective strategy?” are addressed and answered. A decision-analytic approach is employed in this study to assess the payoffs of different possible screening strategies and to suggest an optimal program. For that, an individual-based simulation (microsimulation) model of modular design is developed, which serves as the basis for the subsequent economic appraisal. The following considerations need to be addressed before designing the microsimulation model.

Lung cancer is a non-communicable, i.e. non-transmittable disease, which may be caused by multiple factors. Also, it is non-curable in its late stage. Often the symptoms of lung cancer resemble other obstructive lung diseases which may lead to delays in the diagnosis and a lower survival rate (33). Screening aims to detect cancer in its early more treatable stage in individuals who are at risk but yet show no clinical symptoms, thereby reducing lung cancer mortality. The main health risk, which is linked to the onset of malignancy in the lungs, is an intensive exposure to tobacco, which is clinically quantified as pack-years. Therefore, smoking behaviour was included as the major hazard predictor and a selection factor for the screening.

At the time of the study, two ongoing clinical trials of lung cancer screening with CT present their findings: the Netherlands-Leuvens Screening Trial (NELSON) in Europe (34) and the National Lung Screening Trial (NLST) in the USA (35). In the trials, the screening strategies comprised of eligible age, exposure to tobacco smoking, screening intervals, and a description of steps on how to proceed with a CT finding, defined in a so-called nodule management protocol (NMP). The clinical trials use different selection criteria and nodule management protocols with different approaches to the quantification of nodules size and growth (which define probable malignancy), numbers of follow-up CT scans, and work-up procedures. The inferences about possible malignancy in NLST are based on the diameter of the nodule and its growth as a 10% increase in the diameter. In NELSON the nodule volume

is assessed and two measures of growth are used: a 25% increase in volume and a growth rate as volume doubling time. The insights on the clinical outcomes of the two different approaches show the importance of the eligibility criteria and the nodule management protocol: comparing to NELSON, NLST reports a greater number of false-positive outcomes. False-positive outcomes and overdiagnosis both lead to redundant diagnostic and therapeutic procedures, which in turn increase costs and reduce the quality of life, constitute harms of screening. Whereas cured cases, decreased mortality and, although not considered in this study, detected other lung diseases are the benefits it provides.

An evaluation of the results of the trials provides sufficient evidence to address the decision problem of whether to implement lung screening or not. However, the consideration of the differences in the outcomes of the two trials makes it difficult to choose an optimal strategy for implementation, to provide a generalisation of the payoffs, as well as to evaluate other possible strategies. These points can be addressed using decision-analytic modelling.

Fine-tuning of a possible screening strategy requires the simulation of variations of the key characteristics as well as the comparison of their positive and negative health outcomes and costs. This depends on the eligible age range, exposure to smoking (pack-years and the maximal number of years since quitting for former smokers), and nodule management protocol (NELSON or NLST approach). For example, the upper limit of the age range of eligibility for screening may reduce the cases of overdiagnosis and the nodule management aids in the interpretation of the results seen during a CT test to determine malignancy.

The choice of a microsimulation model is guided by the gradually progressive course of cancer and its non-transmittable nature, i.e. there is no need to simulate interactions between individuals to represent its epidemiology. In addition, microsimulation models constitute a practical tool for combining information from a wide range of sources, including clinical trials, demographic data, and simulated data. In this study, the model consists of the following six structural modules interacting with each other to represent the epidemiology of lung cancer: natural history, population, clinical detection, survival, screening, and life history.

The natural history module is a reconstruction of the natural course of cancer development mathematically formulated as a set of equations with stochastic assumptions which return individual trajectories from a disease-free state to death. The foundation of the natural history model is the biological two-mutation model of carcinogenesis published by Moolgavkar and Luebeck in 1990 (36). This model comprises of probability generating functions where age, gender and personal exposure to cigarette smoke are translated into the piecewise constant parameters of the hazard functions.

The respective input values are generated by the population module which reconstructs the demography and the smoking behaviour of 10% of the German population over 40 years of

age and produces as output age and exposure to tobacco at each point of time in the simulation. As it is described before, the data of the three RKI surveys are used to elicit the trends of smoking behaviour in the German population and to project them further. The natural history module returns the time (age) of onset of malignancy, the histology of cancer, its growth, lymph nodes involvement, and metastasis – these output values are observed with a time of the event in the model simulation but cannot be observed in reality. These processes are latent and underlying the clinical diagnoses through symptoms in the standard care, which are the observed data.

The module of clinical diagnosis is also formulated as a stochastic process. It is informed by the natural history module and returns the number of diagnosed cases, histology, size, and tumour-node-metastasis stage of cancer. Thereby it adds another step in an individual's trajectory.

The natural history and clinical diagnosis modules include a set of unknown parameters of the distributions used in the model which are not directly observed and therefore need to be fitted. Examples for this are the distribution of the tumour volumes at the time of clinical diagnosis, the distributions of the threshold volumes of lymph nodes involvement, distant metastases as well as age- and cancer type-dependent malignant conversion rates. The data on age and cancer type-specific annual incidental lung cancer are obtained from a population-based survey of 132,612 lung cancer patients conducted in Germany between 2010 and 2012.

The screening module is designed to allow for the fine-tuning of a screening strategy, so it detects as many as possible of the simulated cancers in their earlier stage but minimises the numbers of false positives and overdiagnoses. It comprises of several structural components: eligibility assessment, screening-detection, nodule management (including follow-up), diagnostic work-up, and lung cancer survival. The module is structured to replicate the nodule management protocols of NLST and NELSON, which can be varied in their underlying parameters according to a formulated strategy. The simulation of individual trajectories continues with the screening history, which returns the results of the screening: screen-diagnosed malignancy, its size, stage, and survival outcome. The survival module is a relatively straightforward application of known and observed probabilities of survival based on the cancer stage.

The output values of the microsimulation model for all variations of the screening strategy and the no screening scenario inform the economic model which consists of computation of costs of screening, follow-ups, diagnostic work-ups, and treatment as well as health benefits or harms for each individual in the model over the lifetime horizon. Recommended

discounting is applied in the calculation of the cost-effectiveness ratios (as costs per life-year gained (LYG) in comparison with no program).

The uncertainty is explored by means of one-way sensitivity analyses with varying assumptions about CT sensitivity parameters, parameters of long-term survival after the screening, attendance rate, cost per CT exam, and lifetime treatment costs. The stochastic nature of the developed model and the large population included in the simulation also cover the variation of outcomes due to the uncertainty in the biology of cancer. We, therefore, concentrate on altering the deterministic parameters and documenting variations of effectiveness and cost-effectiveness of the screening strategies. The economic evaluation resulted in two efficiency frontiers which represent weighting two major benefits of screening (LYG and averted lung cancer deaths) against the resulting costs.

We find that the strategy setup of NLST is less efficient than other strategies proposed in our study. We also show that efficient scenarios include the volumetric assessment of the nodule size, i.e. the NELSON approach to the nodule assessment and conclude that changing the threshold values of the volume to 300 mm^3 and the volume doubling time to 400 days would result in a more sensitive NMP. The nodule management protocol is shown to be a critical component in the search for an optimal strategy, which would minimise not only the cost-effectiveness ratio but also balance beneficial and harmful health outcomes. Incremental cost-effectiveness ratios of the efficient scenarios were 16,754–23,847 Euro per life-year gained and 155,287–285,630 Euro per averted lung cancer death, which in general could be considered cost-effective in Germany.

To sum up, the application of the microsimulation model allows optimising the screening strategy, which would otherwise not be feasible within the two major clinical trials. We conclude that the screening would be necessary, effective, and cost-effective; however, careful consideration of the eligibility criteria and the nodule management protocol is required before the implementation of screening in the clinical practice. This model can be further used to evaluate other screening strategies, to consider alternative comparators as well as it can be tailored to examine other hazardous effects such as the exposure to carcinogenetic elements of environmental or occupational origin.

(2) Application of decision-analytic modelling in the evaluation of a vaccination program (article 7)

Vaccination is one of the most effective preventive measures of public health systems. Vaccines can save lives, decrease utilisation of healthcare resources, and improve quality of life. However, not all vaccination programs are economically reasonable. Vaccination policies usually target a large group of a population aiming to reduce the transmission of an infection or prevent complications in the course of the disease, but if the infection is not prevalent in

this group, the introduction of a vaccination against it will require resources without providing sufficient benefits. From another side, even if the prevalence is high enough but the vaccine efficacy is low, it will come to the same inefficient result.

Clinical evidence of efficacy of vaccines is generated in clinical trials, however, comparing to the real settings of the general population where the vaccine is to be introduced, clinical trials cover only a limited sample of the population and may run too short to capture all the effects of a vaccination program. Mathematical models of infectious diseases, which incorporate the evidence generated in clinical trials in their structure, can provide needed generalisations, projections over a longer time horizon, and simulate multiple vaccination alternatives. They provide therefore powerful and useful tools for assessing the epidemiological and the economic impacts. The outputs of adequately built and validated decision-analytic models are valuable for policymakers of national vaccination programs. They provide estimates of morbidity and mortality averted, prevented healthcare resource utilisation and saved quality-adjusted life-years, budget impact, effectiveness and cost-effectiveness output, all necessary inputs in planning, as well as decisions on further additions to the national vaccination policies. In Germany, the Standing Vaccination Committee at the German Robert-Koch Institute (STIKO) is the main decision-making body on the national immunisation programs since August 2006. In the appraisal of and decision on vaccination programs, the Committee uses estimates of disease burden as well as expected epidemiologic and health economic impacts of vaccination alternatives for the German healthcare system. STIKO has issued a methodological paper with guidelines for modelling projections of epidemiologic and health economic effects of vaccinations for decision-making (37). It shows the increasing importance of decision-analytic models in public health policy-making in Germany.

One study included in this thesis is conducted to support the decision-analysis of the STIKO. In the study “Pneumococcal Disease in Adults: a health economics evaluation of various vaccination scenarios in Germany” (Article 7), we address the decision problem about vaccinating German elderly with 13-valent pneumococcal conjugate vaccine (PCV13) which is widely used in children programs but only recently approved for the older population. The STIKO recommends the routine vaccination of children with PCV13 against pneumococcal infections; however, at the time of the study, no recommendation about the elderly vaccination with PCV13 was issued.

The methodology of the analysis adopts a cost-utility approach to evaluate the elderly vaccination with PCV13 and whether it is beneficial for the society to replace the currently recommended 23-valent pneumococcal polysaccharide vaccine (PPSV23). An underlying mechanistic model is required to adequately represent the epidemiological setup of infections

with *Streptococcus pneumoniae* (*S. pneumoniae*) in the German population and the epidemiological impact of the vaccination alternatives.

Pneumococcal infections present modellers with multiple challenges of formulating a mathematical representation of the epidemiological system. These include: (i) the existence of over 90 serotypes of the bacteria with different pathogenic potential and prevalence, (ii) the ability of the bacteria to colonise the nasopharynx of individuals without making them sick, (iii) the transmission via airborne droplets, (iv) the fact that infected and colonised children are the source of transmissions to adults, and (v) the possibility of invasive and non-invasive diseases. Moreover, the dynamic epidemiological system of pneumococcus in Germany has undergone a disturbance induced by the immunisation programs in children, firstly, with PCV7 and then with PCV13. As in other countries, in Germany, childhood vaccinations have led to an indirect decline in invasive and non-invasive infections (caused by the serotypes contained in the applied vaccines) in the unvaccinated adults. This indirect effect is mainly caused by the vaccine-induced reduction in the carriage and the transmission of vaccine serotypes from children to adults. This reduction of the PCV7-serotypes created an ecological niche which serotypes not covered by the vaccine were able to occupy, leading to a considerable increase in infections attributable to non-vaccine serotypes. These two opposing effects are known as herd immunity effect and replacement effect induced by a large-scale vaccination. The indirect effects of the childhood immunisation program are observed in the data on the elderly where the incidence of vaccine-preventable infections has decreased and, as a consequence, so has the potential beneficial effects of the introduction of the same vaccine in the elderly. The indirect effects observed in the epidemiology strongly influence the outcomes of the cost-effectiveness assessment. Therefore, a dynamic transmission model is adopted to represent the epidemiology of *S. pneumoniae* in the German population. Transmission models incorporate interactions between individuals and allow the modelling of dynamics of serotype competition for the colonisation, herd immunity and replacement effects as well as the natural course of infection. The structure comprises of the following compartments or states where the modelled population spends its modelled time governed by rules of transitions between them: (i) susceptible, (ii) colonised carriers of one or two serotype groups, (iii) cleared of carriage, (iv) infectious, (iv) invasive or non-invasive diseased, (iv) recovered and, (v) dead. The vaccination is modelled as a reduction of the probability to be ill from invasive or non-invasive diseases caused by the vaccine-covered serotypes. According to the current knowledge, the vaccine protection is modelled to wane over time which corresponds to the inverse of the expected duration of immunity.

The population is of a simplified structure and modelled as 400 age classes, each containing 100,000 individuals who age each quarter at the same point in time. Given the complexity of

the epidemiological model, the simplified population structure, as well as the grouping of the serotypes, are required to create a steady-state with a reasonable computational effort. The transmission probability is governed by a so-called force of infection function, which represents “effective” contact rates between the compartments leading to colonisation or infection. The demographic contact rates are estimated using the statistical approach of generalised additive models with thin plate regression splines as the smoothing term using the contact data collected within a large survey conducted in Europe (38). The parameters which model the effective contact, i.e. transmission of infection per contact cannot be observed and have to be elicited through the fitting of the model to the observed incidence data using Markov chain Monte Carlo method. The mathematical formulation comprises of a large system of ordinary differential equations which can be solved using numerical methods.

The developed epidemiological model simulates the carriage states, the direct and indirect effects of the childhood vaccination with PCV7 in the years 2004 to 2009 and consequently with PCV13 in 2010 till 2015 as well as the direct effects of alternative vaccination scenarios on the epidemiology in the elderly. The results are age- and serotype-specific pneumococcus carrier prevalence and incidences of pneumococcal infections as functions of time.

The epidemiological output values for different vaccination strategies serve as inputs into the consequent health economic analysis. The age-specific numbers of infections are used to calculate and predict over the lifetime horizon the number of invasive and non-invasive cases, hospitalisations, disease-caused deaths, (discounted) quality-adjusted life-years gained, healthcare utilisation, total costs for each program, as well as cost-effectiveness ratios using the current program with PPSV23 as a central comparator. To further assist the STIKO in the decision process, additional measurements of vaccination performance are computed. These include number needed to vaccinate to prevent one case of infection or disease-related death, the impacts of the age at vaccine administration, and the impact of the frequency of revaccination on the outcomes.

The results suggest that, in terms of effectiveness, the vaccination scenario of PPSV23 being followed by vaccination with PCV13 (sequential vaccination) would have the largest preventive effect on the infections and deaths. Meanwhile, the vaccination with PPSV23 would be more efficient based on the number needed to vaccinate in order to prevent one pneumococcal infection or one death. The economic analysis shows that using PPSV23 for the vaccination would require considerably fewer resources and costs than the sequential scenario. Moreover, for PCV13 due to the weaker effects through herd immunity and its higher price, using PCV13 in the vaccination of the elderly (77,000-92,000 Euro/QALY gained) is considered not cost-effective compared to the vaccination with PPSV23 (36,000-38,000 Euro/QALY gained). Additional analyses of the frequencies of revaccination suggest

that the implementation of a revaccination scheme would be more efficient. In conclusion, the economic evaluation suggests that vaccination with PPSV23 at age 60 being followed by periodic revaccination with PPSV23 every six years after the initial vaccination should be the preferred strategy. Based on the evidence, the STIKO currently recommends this vaccination program for the elderly in order to prevent pneumococcal infections (39).

Future directions for research should include studies which evaluate the vaccines that are currently being developed as well as represent the pneumococcal epidemiology more detailed. The recent epidemiological data suggest that a few serotypes (e.g. 3 and 19A) (40, 41) which are covered in PCV13 persist and are less affected by the vaccination in children. Accurate representations would require the modelling of the epidemiology of these serotypes separately from the others and would need data on the serotype-specific carriage and infection incidences. Additionally, this study points out the necessity of observational studies to examine in greater detail the vaccine effectiveness against non-invasive pneumococcal diseases. The availability of data will facilitate more accurate decision-modelling and the implementation of more effective vaccination strategies.

C. Application of decision-analytic modelling in health economic evaluations

(1) Application of decision-analytic models as a basis for health economic evaluations (article 8)

Although the application of decision-analytic modelling has become widespread in health technology assessments (HTA), in Germany, the use of DAM is not yet required for decision-making in the healthcare sector. In the study “The Role of decision-analytic modelling in German health technology assessments” (Article 8), we examine the application of decision-analytic models, and its impact on the evidence provided in HTA reports published by the German Institute of Medical Documentation and Information (DIMDI) – one of two leading HTA organisations in Germany. The second organisation is the Institute for Quality and Efficiency in Healthcare (IQWiG) which at the time of our study did not carry out economic evaluations. Therefore, we did not consider its database. In this review, 107 HTA reports published between 1998 and 2012 are examined for the purpose of assessing the quality of the conclusions they provide. In this selection, 17 HTAs applied DAM for the economic evaluation and, compared to others, report evidence of higher relevancy for decision-making. Additionally, 24 studies of a lower quality point out that the application of DAM would likely improve the relevancy of the evidence provided in the respective economic evaluation. Indeed, the use of an appropriate model may allow estimating a wide range of outputs that

may in turn influence decisions about the program implementation, resource allocation or provide the basis for future research. We also examine the developed decision-analytic models in the selected 17 HTAs and conclude that the applied methods differ in the dimensions of economic analyses (such as perspective, measures of effectiveness, discounting, and sensitivity analyses) probably due to the absence of methodological requirements on the part of DIMDI.

(2) Validity of evidence for decision-making produced using decision-analytic-modelling in economic evaluations (article 9)

This section continues the discussion about the application of decision-analytic models for the assessment of vaccination programs. Although decision-analytic models have been widely applied in health economic evaluations of vaccines, comparatively little attention has been paid to the issues around potential biases and misleading interpretations they may evoke.

In the study "Cost Effectiveness of Elderly Pneumococcal Vaccination in Presence of Higher-Valent Pneumococcal Conjugate Childhood Vaccination: Systematic Literature Review with Focus on Methods and Assumptions" (Article 9), we review and summarise the results of modelling studies which evaluate the cost-effectiveness of the elderly vaccination against pneumococcal infections. Additionally, we assess the validity of these studies based on the assumptions and methods the researchers apply in the construction of their decision-analytic models. This study is motivated by ongoing debates around the cost-effectiveness of the elderly vaccination with PCV13 which continues even after the clinical trial "Community-Acquired Pneumonia Immunization Trial in Adults" (CAPiTA), which presents its results about the efficacy of PCV13 in the elderly. In contrast to earlier studies, several recently published economic evaluations demonstrate that PCV13 may not be cost-effective when children are routinely vaccinated with higher-valent pneumococcal conjugate vaccines such as PCV10 and PCV13. We look at the economic evaluations which have been published after the results of CAPiTA and aim to gain an insight into the driving factors for differences in the respective conclusions. We separately examine the assumptions and inputs of the mechanistic models which simulate the epidemiological setup as well as of the economic models which weight the costs against the benefits of alternative strategies. Both directly drive the outcomes of cost-effectiveness analyses; however, the former can be easily overlooked when interpreting the results of the analyses.

In order to assess the validity of the authors' respective methodological choices for the epidemiology, we conceptualise key components of a model for the epidemiological setup of *S.pneumonia* and its changes over time, namely the impact of routine immunisations of

children on the vaccine-preventable infections in the adult population, i.e. indirect effects, and the duration of vaccine protection in vaccinated adults (Figure 3).

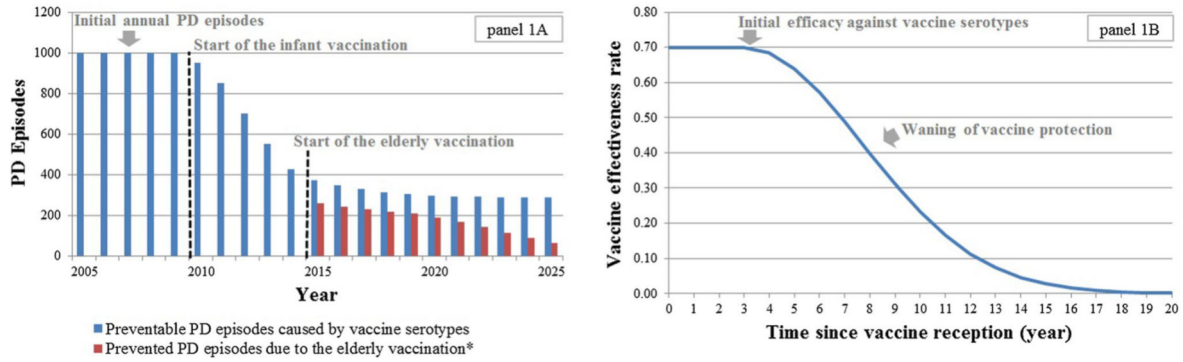

Figure 3: Constituents of the vaccination effects over time: a graphical representation.
The outcomes of the elderly pneumococcal vaccination depend on the initial vaccine effectiveness against vaccine-type pneumococcal diseases (PD) and its protection over time (illustrated in B) and the PD incidence caused by vaccine-type serotypes over time, which is also influenced by the indirect effects of childhood vaccination with PCV (illustrated in A). Asterisk: vaccination rate assumed to be 100% and vaccine effectiveness, according to B.
Source: Article 9, Figure 1.

The combination of these two integrals majorly drives the epidemiological system and the outcomes of the vaccination. The indirect effects of the childhood program include the herd immunity, which impacts not only infections in the children but also in the adults with whom the vaccinated children have contact. The herd immunity reduces the probability of transmitting the bacteria to the adults and leads to an indirect decrease in the incidence (see Figure 3, panel A). Although it does not make the adults immune to the infection, the herd immunity provides indirect protection and makes the direct vaccination less effective: the number needed to vaccinate in order to prevent one case becomes higher, which translates to higher costs needed to provide additional benefit. Therefore, a thorough investigation of the underlying epidemiological outlook in the population is highly important before devising a model which is supposed to accurately represent it. In this review, we find several methodological approaches to reproduce the herd immunity effects of childhood vaccination.

Although the incidence rates of infections with *S.pneumonia* are comparatively well-reported and analysed, the reconstruction of the epidemiology in a model is complicated. This is due to numerous uncertainties in the interconnecting elements of the infection transmission and its spreading, which are not directly observed and measured.

To begin with, there exist over 90 different strains (serotypes) of *S.pneumonia*, with several of them having a higher potential to cause the disease and a higher prevalence in the susceptible groups. Thirteen of them constitute antigens in PCV13 and 23 in the PPSV23 vaccine. The epidemiological surveillance rarely provides numbers on prevalence and incidence of each serotype, therefore, modelling the serotype-specific epidemiology is very challenging, and researchers usually combine them into vaccine- and non-vaccine types for

modelling purposes. Another factor which complicates the modelling is the data we observe, i.e. the surveillance data commonly records the disease cases but not the infections and the carriage. In contrast, a dynamic-transmission model represents the epidemiological circulation and the transmission process (including herd immunity) which leads to the cases of the disease. The types of models, which do not simulate interaction, do not include the indirect effects of the childhood vaccination in their structure which results in assumptions having to be made. Under these circumstances, the separation of the serotypes, i.e. a serotype-specific approach, plays a crucial role, because when assuming an indirect reduction in the vaccine-preventable incidence in the adults due to the childhood program it is reasonable to suggest that this reduction only occurs in the cases caused by the types which are included in the childhood vaccine. The time-varying decrease of the vaccine-preventable serotypes in the overall serotype distribution is not accounted for in serotype non-specific approach, which, therefore, would lead to a considerable underestimation of the herd immunity.

On the other hand, vaccine efficacy and its protective impact (Figure 3, panel B) directly define the number of preventable cases which in turn translates into vaccination-preventable costs of care and quality of life impairment. CAPiTA provides clinical evidence for PCV13 vaccine efficacy and its stable protection over five years in adults over 60 years of age. However, the follow-up period is too short to capture the full length of the protective effects of the vaccine. Therefore, the modelling of the protective effects, i.e. the duration of the protection, is subject to assumptions. Additionally, CAPiTA provides little evidence about the age-dependency of the vaccine efficacy. Thus, assumptions for the age-dependency of the vaccine efficacy and for the duration of the protection of PCV13 are examined in our review. In order to be able to compare these assumptions, we define a measure that reproduces the total protective effect of the vaccine – the expected vaccine protection over time (EVPOT). It is calculated by integrating the years of protection adjusted for the vaccine efficacy at a given point in time which is represented by a waning curve. EVPOT is measured in efficacy-adjusted protection years (EAPY) and quantifies the assumption about the initial vaccine efficacy and the waning of its protection in one number, which makes comparative analyses and visualisations easier. Figure 4 represents a variety of approaches to the modelling of vaccine protection that the authors used. Some studies simulate EVPOT of 3.75 EAPY and some of over 15 EAPY.

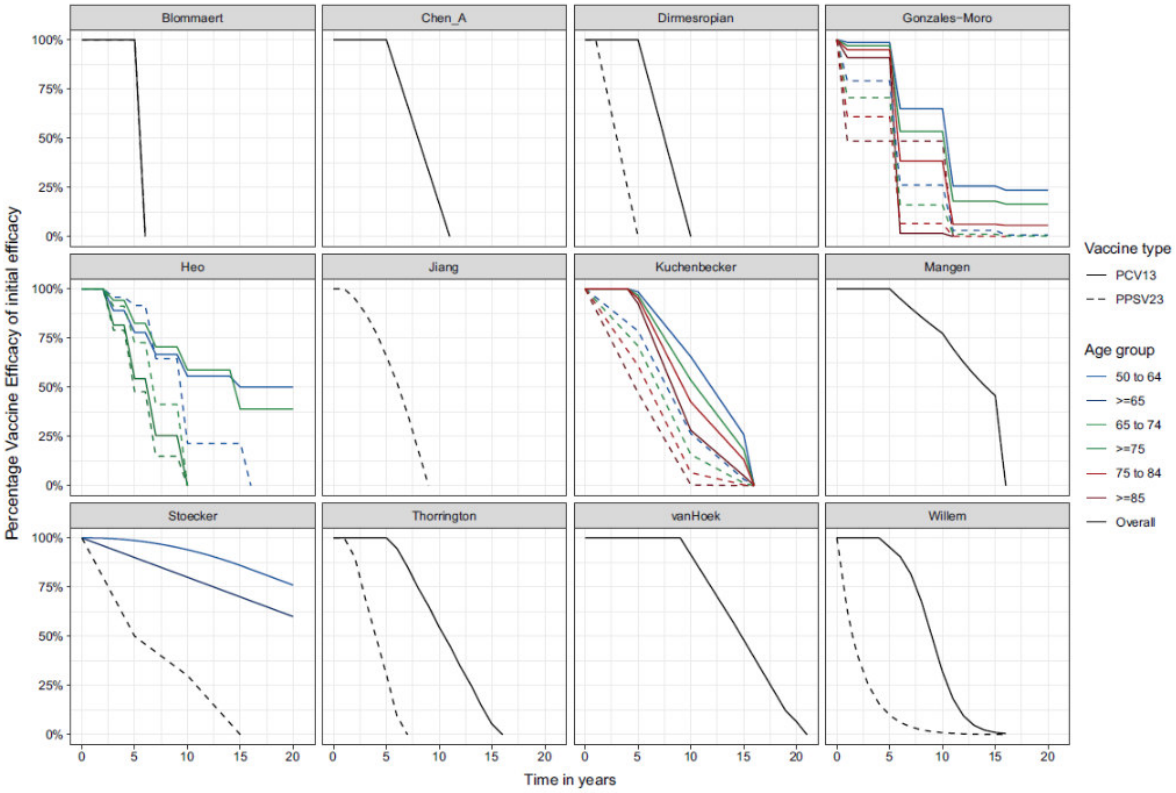

Figure 4: Representation of constructed waning patterns reported in the selected studies by the first author, vaccine, and age group (when reported).
Source: Article 9, Figure 3.

The methodological choices in modelling the herd immunity and the vaccine protection over time along with every key dimension of the economic evaluation are summarised and assessed in terms of transparent and complete reporting as well as relevancy and validity for decision-making. The detailed assessment is conducted using the “Evidence and Value: Impact on DEcisionMaking”(EVIDEM) (42) instrument which is adapted to the goals of the review where the section devoted to the parameters and methods is extended to assess the validity of the methodological choices made for the modelling of the epidemiological setup and vaccination effects over time. EVIDEM allows for transparent work of the reviewers and provides a framework for the assessment of the quality of the economic evaluation across its key dimensions. We use its scoring system to categorise the evaluations into the higher and lower quality and report the cost-effectiveness estimates provided by the studies of higher validity. Four out of 13 studies are considered of lower quality, i.e. the derived conclusions are judged to be questionable and misleading due to the applied methodological choices and assumptions. Three of these studies assess the cost-effectiveness of PCV13 in the elderly and conclude that PCV13 was highly cost-effective under the ongoing herd effects of the childhood program with PCV13. These studies are seen to underestimate the indirect reduction of the incidence due to the PCV13 program in children and possibly, in combination with the assumption of longer vaccine protection, to overestimate the benefits of

the elderly vaccination. Although these evaluations are funded by the industry, we could not elicit a funding bias because other studies, which are also industry-supported, are of a higher quality. We consider the other nine studies to be fit for the purpose of vaccine evaluation and summarise their results. These results, however, do not provide a straight forward conclusion and an overall agreement that the usage of PCV13 in the elderly is cost-effective, but they suggest that the outcomes cannot be easily translated from one epidemiological setting to another and are driven by the predictions of the pneumococcal disease incidence and the estimates of the pneumococcal vaccine effectiveness over time.

Although within the scope of the review, we cannot elicit a relative contribution of each factor, we emphasise the importance of understanding of the methods and assumptions applied in the modelling behind the economic calculations. Numerous uncertainties and methods to address them have to be well communicated to decision-makers.This would require the authors to provide a transparent report of their work and to properly validate their models. Without properly conducted adequate justification of the applied methods, inputs, and assumptions, there is little basis for decision-makers to have confidence that the results of the decision-analytic models are credible and can be used in healthcare decisions.

3. Results and outlook on further research needs

Currently, the healthcare sector collects and possesses an increasing amount of observable data on healthcare production, insurance services, epidemiological surveillance, clinical research, and social processes. Decision-makers constantly face a challenging task of navigating through the emerging evidence while it is the task of researchers and practitioners of health economics to provide them support in evidence-based rational decision-making. Health economics possesses a wide spectrum of methods and techniques which can be used in a variety of decision-making problems. On the one hand, the application of statistical methods to healthcare data allows synthesising evidence and putting it together in a comprehensible way in order to devise clinical practices and public health policies. Methods of health economic evaluation in conjunction with decision-analytic modelling, on the other hand, integrate new evidence and observable data from a wide range of sources into one framework which enables a comparative analysis of alternative healthcare interventions in terms of both their costs and health benefits. Health economic evaluations result in estimations of the effectiveness of different courses of action and offer strategies with the best value for the money.

The present thesis demonstrates the importance and capability of statistical and decision-analytic modelling methods in generating evidence for rational decision-making in healthcare policy. Each study in this collection contributes to the current and future debates around the studied interventions as well as into the discussions about methods and study designs. Each paper includes a transparent reporting and rationale for the applied methods. The two papers which include decision-analytic modelling using complex methods describe the model structure, parameterisation, calibration of unknown parameters, and uncertainty analyses in great detail.

The methodological approaches and results of the included studies contribute to answering the formulated research questions.

> *What is the contribution of statistical models in the synthesis of evidence for health economic evaluations and decision-making in public health and the healthcare sector?*

This thesis contains examples of quantitative analyses starting with a simple descriptive analysis and ending with complex computational statistics. As it is shown, a mere description of a collected dataset has limits in its production of knowledge. Although observations are made and described, connecting these observations into an interpretation depends upon the application of inference statistics. Inference statistics offers a large variety of methods to analyse data of different types, whereas choosing the right approach determines the accuracy of the resulting explanatory or predicting statements. The datasets analysed in the present thesis stem from large population-level surveys (Article 1), international surveys with

self-reported questionnaires (Article 3), a multicentre prospective observational survey (Articles 4 and 5), and online interviews (Article 2). The analysed dependent and predictor variables vary in their nature; however, they can be seen as merely numerical or categorical vectors characterised by a certain statistical distribution, including concentrated values and influential outliers.

For example, the two studies, which address smoking behaviour, examine datasets where the outcomes of interest are a measurement of the likelihood of an action, i.e. staring and quitting smoking at a certain age (Article 1) and of being willing to use and to pay for aid to cease (Article 2). Logistic regression models are applied in these studies to analyse the patterns in the data. The combination of the findings of these two studies may contribute to designing a policy which aims at a reduction or prevention of cigarette smoking. Policymakers can consider the fact that Germans at the age between 16 and 18 are likely to start smoking. Development of a preventive program could include, for example, an introduction of educative measures about the hazardous effects of tobacco consumption in this age group before the behaviour becomes addictive and more difficult to manage. Additionally, aiming at reducing the size of the peer group, as shown in the other study (Article 2), might increase the probability of a young smoker to use a smoking cessation aid.

Two other studies (Articles 4 and 5) demonstrate the application of generalised linear models in the analyses of cost and quality of life data in HIV care. Both costs of care and quality of life outcomes are not normally distributed. The former due to a small part of the patients having high costs of treatment and the latter due to the measurement scale from 0 to 1. Not appropriately controlling for the nature of the data in the application of regression models leads to inaccurate information. In these studies, generalised linear models are used, which give a framework for the analyses of not normally distributed data of the costs and utility values without a transformation. The findings allow for an understanding of the influential factors and can contribute to the development of better HIV management programs. For example, (i) improving the adherence to medication and prescription of a medically justified NNRTI-based treatment could save costs, (ii) the development of treatment guidelines, which recommend the initiation of cART even in asymptomatic patients with normal CD4-T cell counts may reduce both the costs and quality of life impairment. They also contribute to the understanding of common methodologies used to address health economic data such as the utilisation of healthcare resources, costs and quality of life as well as provide detailed estimates of the cost of the disease and utility values which can be an important basis for the implementation of future health economic evaluations in the field of HIV care and prevention.

These papers, therefore, show that the findings obtained using appropriate comprehensive statistical analyses can produce more information than just observing the data and can be of

value for clinical practice and policy-making. However, it is to be noticed, that when the data are incomplete or collected with shortcomings, the application of statistical analyses is limited in the answers it may provide. For example, the CORSAR survey does not include patients who are naïve to cART, making it impossible to investigate health-related quality of life and the costs in this group (Articles 4 and 5). Further, in the study which investigates smoking cessation aids the survey does not incorporate participants from higher age groups due to resource limitations resulting in a sample which is not representative for the German population (Article 2). From another side, the study which is based on three large population surveys conducted by the RKI also contains a bias despite its large sample size (Article 1). This bias originates from the inclusion of older people who are likely to be healthier because they survived until the beginning of the survey. The inclusion of these people in the statistical modelling can result in an underestimation of the prevalence of smokers in the early cohorts. Therefore, consideration of the statistical methods which are to be applied to analyse the data should be included in the planning of an observational study in the early stage along with the formulation of the policy-relevant research questions.

What are the capabilities of decision-analytic modelling to synthesise evidence about complex public health interventions?

Two studies which provide economic evaluations of two preventive public health measures – screening (Article 6) and vaccination (Article 7) – show the capacity of decision-analytic models to integrate data stemming from different sources into a system which simulates and extrapolates the epidemiological and economic effects of the interventions. The flexibility of the models facilitates comprehensive comparative analyses of alternative courses of action, using different health outcomes and comparators as well as examining the uncertainty of the results by varying input values. Using current clinical, epidemiological, biological, and demographic knowledge, we construct (i) an individual-based simulation model for the economic evaluation of a screening program to prevent lung cancer morbidity and mortality among smokers (Article 6), and (ii) a dynamic-transmission model for the evaluation of a vaccination program against pneumococcal infections in the elderly in Germany (Article 7). The availability of health economic inputs allows the estimation of the economic effects of the interventions across various comparative scenarios and uncertainty analyses. The elaborated models also facilitate fine-tuning the interventions and generalisation of their outcomes over the population groups and time horizons beyond the settings of the clinical trials. The findings of the economic evaluation of the screening have a great capability to guide policy-making in lung cancer prevention, whereas the economic evaluation of the elderly vaccination has been used in decision-making by the STIKO in her recommendation on pneumococcal vaccination. Although the developed decision-analytic models are highly comprehensive, they may be further improved and developed. With the collection of new

epidemiologic and economic data, the models are to be updated to provide new predictions and include new scenarios. Additionally, structural uncertainty analyses have not been provided in these evaluations. In the modelling of infectious diseases (Article 7), individual-based models can be applied to reproduce the stochasticity of individual contacts and disease transmission. However, the development of such a model would require more data on contacts (e.g. within households, weather dependent, etc.), demography and epidemiology. The current model for lung cancer screening does not include a treatment module and contains only life-years gained as the measure of health outcomes. The inclusion of the costs and quality of life data in the patients treated for lung cancer will produce a better representation of the reality and new estimates of cost-effectiveness.

Does decision-analytic modelling as an instrument of health economic evaluations advance evidence synthesis for rational decision-making in public health and the healthcare sector?

The review and analysis of DIMDI's HTA reports demonstrate that the relevancy and validity of technology assessments can be increased by including a decision-analytic model into the economic analysis (Article 8). It is, however, important to note that the development of a (complex) decision-analytic model involves structural and parametrical assumptions which can be decisively influential on the final outcomes and the message being given to the policymakers. As it is demonstrated in the review of decision-modelling based economic evaluations of the elderly pneumococcal vaccination programs (Article 9), the assumptions about vaccine effectiveness, duration of protection, choices of modelling the herd immunity, and the replacement effect determine the output values of the epidemiological models. Additionally, to the epidemiological outcomes, input values used in the economic analysis directly drive the estimates of cost-effectiveness. Therefore, careful consideration and justification of the chosen methods and assumptions, as well as a detailed investigation of structural uncertainty are necessary before reporting an evaluation which is intended to inform decision-making. When inaccurate and invalid assumptions are made in the structure, and for the input values, decision-analytic models become misleading instruments rather than powerful supporting tools and the message being communicated to decision-makers becomes of low value. In summary, it can be stated that decision-analytic modelling provides methods of great capacity in facilitating decision-analyses and supporting policy-making in Germany.

Overall, statistical and decision-analytic models have become indispensable in health economic studies. Further production of knowledge relies on the availability and quality of the data. Although current data collected in Germany give an opportunity for comprehensive analyses in some areas, others stay less observed and analysed. Further improvement of

the surveillance systems, data collection, storage, and availability for research are required. The currently starting “age of big data” in the healthcare sector also requires a comprehensive mastering of the methodologies for research.

Further development of mathematical methods and techniques of computational statistics, as well as biological and epidemiological knowledge, demand interdisciplinary approaches which go beyond the specialisation of individual disciplines. For example, developments in the field of mathematical biology can bring techniques for modelling cancers of various biology or approaches of molecular epidemiology can allow integrating the variation between different epidemics caused by shifts in viral genetics. Given the growing complexity of methods and the integration of a large range of data sources in healthcare, it is imperative for researchers to provide a transparent communication of the methods and assumptions on which their inferences are based. In turn, decision-makers should have a good understanding of the principles and the decision-analytic-modelling methods currently used in economic evaluations. Furthermore, the increasing methodological complexity will require advancing the knowledge and the competence of the decision-making bodies. This will improve critical appraisal of the developed models, allow rational decision-making, and optimised channelling of limited resources. Additionally, provided the existence of continuous technological progress in the healthcare and the growing demand for healthcare services, the methods of health economics will be required to provide possibilities for conducting studies which are not only directed to the achievement of technical and productive efficiency but also allocative efficiency, i.e. to generate a framework for decision-analyses across multiple interventions which target varying health conditions.

4. Literature cited

1. HakemZadeh F. Evidence-Based Policy-Making in Canada Edited by ShaunP. Young Oxford University Press (2013) 226 pp. ISBN: 97800199003037. Can J Adm Sci 2014; 31(3):214–5.

2. Mills AJ, Durepos G, Wiebe E. Encyclopedia of case study research. Los Angeles [Calif.]: SAGE Publications; 2010.

3. Rutter H, Savona N, Glonti K, Bibby J, Cummins S, Finegood DT et al. The need for a complex systems model of evidence for public health. The Lancet 2017; 390(10112):2602–4.

4. Group TCSM, Staff AMS. Modelling in Healthcare. Providence, RI: American Mathematical Society; 2010. Available from: URL: http://gbv.eblib.com/patron/FullRecord.aspx?p=4715700.

5. Jones AM. Applied econometrics for health economists: A practical guide. 2. ed., repr. Oxford: Radcliffe; 2009.

6. Kuntz K, Sainfort F, Butler M, Taylor B, Kulasingam S, Gregory S et al. Decision and Simulation Modeling in Systematic Reviews. Rockville (MD); 2013.

7. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2011. (Handbooks in health economic evaluation series). Available from: URL: http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=1689059.

8. Sanson-Fisher RW, Bonevski B, Green LW, D'Este C. Limitations of the randomized controlled trial in evaluating population-based health interventions. Am J Prev Med 2007; 33(2):155–61.

9. Rescigno A, Thakur AK, editors. New Trends in Pharmacokinetics. Boston, MA: Springer US; 1992.

10. Afzali HHA, Karnon J. Exploring structural uncertainty in model-based economic evaluations. Pharmacoeconomics 2015; 33(5):435–43.

11. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. J Health Serv Res Policy 2004; 9(2):110–8.

12. O'Mahony JF, Newall AT, van Rosmalen J. Dealing with Time in Health Economic Evaluation: Methodological Issues and Recommendations for Practice. Pharmacoeconomics 2015; 33(12):1255–68.

13. Sun X, Faunce T. Decision-analytical modelling in health-care economic evaluations. Eur J Health Econ 2008; 9(4):313–23.

14. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004; 8(36):iii-iv, ix-xi, 1-158.

15. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making 2012; 32(5):722–32.

16. Hens N, Shkedy Z, Aerts M, Faes C, van Damme P, Beutels P. Modeling infectious disease parameters based on serological and social contact data: A modern statistical perspective. New York, N.Y.: Springer; 2012. (Statistics for biology and health2012: 1).

17. Donald W. Boyd. Systems Analysis and Modeling: Elsevier; 2001.

18. Walker DG, Wilson RF, Sharma R, Bridges J, Niessen L, Bass EB et al. Best Practices for Conducting Economic Evaluations in Health Care: A Systematic Review of Quality Assessment Tools. Rockville (MD); 2012.

19. Langlois ÉV, Daniels K, Akl EA. Evidence synthesis for health policy and systems: A methods guide. [S.l.]: World Health Organization; 2018.

20. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012; 380(9859):2224–60.

21. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012; 380(9859):2095–128.

22. Wood SN. Thin Plate Regression Splines. Journal of the Royal Statistical Society. Series B (Statistical Methodology) 2003; 65(1):95–114. Available from: URL: http://www.jstor.org/stable/3088828.

23. Holford TR, Levy DT, McKay LA, Clarke L, Racine B, Meza R et al. Patterns of birth cohort-specific smoking histories, 1965-2009. Am J Prev Med 2014; 46(2):e31-7.

24. Bayoumi AM. The measurement of contingent valuation for health economics. Pharmacoeconomics 2004; 22(11):691–700.

25. Swindell WR. Accelerated failure time models provide a useful statistical framework for aging research. Exp Gerontol 2009; 44(3):190–200.

26. Groeneboom P, Wellner JA. Information Bounds and Nonparametric Maximum Likelihood Estimation. Basel: Birkhäuser Basel; 1992.

27. Lund JL, Yabroff KR, Ibuka Y, Russell LB, Barnett PG, Lipscomb J et al. Inventory of data sources for estimating health care costs in the United States. Med Care 2009; 47(7 Suppl 1):S127-42.

28. Leggett LE, Khadaroo RG, Holroyd-Leduc J, Lorenzetti DL, Hanson H, Wagg A et al. Measuring Resource Utilization: A Systematic Review of Validated Self-Reported Questionnaires. Medicine (Baltimore) 2016; 95(10):e2759.

29. Malehi AS, Pourmotahari F, Angali KA. Statistical models for the analysis of skewed healthcare cost data: a simulation study. Health Econ Rev 2015; 5:11.

30. Moran JL, Solomon PJ, Peisach AR, Martin J. New models for old questions: generalized linear models for cost prediction. J Eval Clin Pract 2007; 13(3):381–9.

31. Robert A. Rigby, Mikis D. Stasinopoulos, Gillian Z. Heller, Fernanda De Bastiani. Distributions for modelling location, scale, and shape: using gamlss in r. [S.l.]: CRC PRESS; 2019.

32. Degroote S, Vogelaers D, Vandijck DM. What determines health-related quality of life among people living with HIV: an updated review of the literature. Arch Public Health 2014; 72(1):40.

33. Ellis PM, Vandermeer R. Delays in the diagnosis of lung cancer. J Thorac Dis 2011; 3(3):183–8.

34. Horeweg N, Scholten ET, Jong PA de, van der Aalst CM, Weenink C, Lammers J-WJ et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified

analysis of screening test performance and interval cancers. The Lancet Oncology 2014; 15(12):1342–50.

35. van der Aalst CM, Haaf K ten, Koning HJ de. Lung cancer screening: latest developments and unanswered questions. The Lancet Respiratory Medicine 2016; 4(9):749–61.

36. Moolgavkar SH, Luebeck G. Two-Event Model for Carcinogenesis: Biological, Mathematical, and Statistical Considerations. Risk Analysis 1990; 10(2):323–41.

37. STIKO. Methoden zur Durchführung und Berücksichtigung von Modellierungen zur Vorhersage epidemiologischer und gesundheitsökonomischer Effekte von Impfungen für die Ständige Impfkommission, Version 1.0: Robert Koch-Institut; 2016 [cited 2019 Aug 18]. Available from: URL: https://www.rki.de/DE/Content/Kommissionen/STIKO/Aufgaben_Methoden/Methoden_Modellierung.pdf%3F__blob%3DpublicationFile.

38. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008; 5(3):e74.

39. STIKO. Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch-Institut – 2017/2018; 2017 [cited 2019 Aug 18]. Available from: URL: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2017/Ausgaben/34_17.pdf?__blob=publicationFile.

40. Southern J, Andrews N, Sandu P, Sheppard CL, Waight PA, Fry NK et al. Pneumococcal carriage in children and their household contacts six years after introduction of the 13-valent pneumococcal conjugate vaccine in England. PLoS ONE 2018; 13(5):e0195799.

41. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis 2018; 18(4):441–51.

42. Goetghebeur MM, Wagner M, Khoury H, Levitt RJ, Erickson LJ, Rindress D. Evidence and Value: Impact on DEcisionMaking--the EVIDEM framework and potential applications. BMC Health Serv Res 2008; 8:270.

5. Articles included in the cumulative doctoral thesis

	Articles included in the cumulative doctoral thesis	Status	VHB-JOUR-QUAL3/ Impact Factor/ SJR rating
Articles included in section A			
1	**Treskova M**, Aumann I, Zeiher J, Lange C, Kuhlmann A. Estimation of age -, gender - and birth cohort-specific parameters of smoking behaviour for the German population.	Submitted to Tobacco Use Insights	No rating 1.71 No rating
2	Aumann I, **Treskova M**, Hagemann N, Graf von der Schulenburg J-M. Analysis of Driving Factors of Willingness to Use and Willingness to Pay for Existing Pharmacological Smoking Cessation Aids Among Young and Middle-Aged Adults in Germany. Appl Health Econ Health Policy. 2016;14:441-52. doi:10.1007/s40258-016-0239-0.	Published in Applied Health Economics and Health Policy	B 2.664 32
3	Kuhlmann A, Schmidt T, **Treskova M**, Lopez-Bastida J, Linertova R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe. Eur J Health Econ. 2016;17 Suppl 1:79-87.doi:10.1007/s10198-016-0786-1.	Published in The European Journal of Health Economics	B 2.169 45
4	**Treskova M**, Kuhlmann A, Bogner J, Hower M, Heiken H, Stellbrink H-J, et al. Analysis of contemporary HIV/AIDS health care costs in Germany: Driving factors and distribution across antiretroviral therapy lines. Medicine (Baltimore). 2016;95:e3961. doi:10.1097/MD.0000000000003961.	Published in Medicine (Baltimore)	No rating 1.870 No rating
5	**Treskova M**, Scholz S, Kuhlmann A, Mahlich J, Stoll M. Estimation of utility values and factors driving health-related quality of life in people living with HIV and AIDS and receiving cART in Germany: analysis of a cohort study.	Submitted to Applied Research in Quality of Life	No rating 1.528 25
Articles included in section B			
6	**Treskova M**, Aumann I, Golpon H, Vogel-Claussen J, Welte T, Kuhlmann A.Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting. BMC Med. 2017;15:162. doi:10.1186/s12916-017-0924-3.	Published in BMC Medicine	No rating 9.428 108
7	Kuhlmann A, **Treskova M**, Graf von der Schulenburg J-M. Pneumococcal Disease in Adults: a health economics evaluation of various vaccination scenarios in Germany. Robert-Koch-Institute, 2016. Available at https://www.rki.de/DE/Content/Infekt/Impfen/Forschungsprojekte/abgeschlossene_Projekte/Pneumokokkenerkrankungen/Abschlussbericht.html	Published on Robert-Koch-Institute website. Paper in progress	No rating No rating No rating
Articles included in section C			
8	Kuhlmann A, **Treskova M**, Braun S, Graf von der Schulenburg J-M. The Role of decision-analytic modelling in German health technology assessments. Health Econ Rev. 2015;5:7. doi:10.1186/s13561-014-0039-x.	Published in Health Economics Review	No rating 1.374 18
9	**Treskova M**, Scholz S, Kuhlmann A. Cost Effectiveness of Elderly Pneumococcal Vaccination in Presence of Higher-Valent Pneumococcal Conjugate Childhood Vaccination: Systematic Literature Review with Focus on Methods and Assumptions. PharmacoEconomics. 2019 https://doi.org/10.1007/s4027 3-019-00805 -5.	Published in Pharmaco Economics	A 3.705 91

Article 1

Estimation of age-, gender- and birth cohort-specific parameters of smoking behaviour for the German population

Treskova M, Aumann I, Zeiher J, Lange C, Kuhlmann A

Submitted to Tobacco Use Insights

2019

Estimation of age-, gender- and birth cohort-specific parameters of smoking behaviour for the German population.

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Abstract:

Introduction and Aims: The prevalence of smokers in a population is an essential indicator of public health. Current literature lacks studies which capture smoking history summaries for different birth cohorts in Germany. This study estimates the age- and birth cohort-specific cigarette smoking patterns for Germany.

Design and Methods: Data are obtained from cross-sectional surveys conducted in 1997–2012 in Germany. Parameters of smoking behaviour were statistically estimated for the German 1920–1980 birth cohorts and projected up to the year 2025. Estimated parameters include age- and cohort-specific smoking initiation probability, smoking cessation probability, current and former smokers' prevalence, and smoking intensity. Thin plate regression splines and cumulative logistic models were applied.

Results: Smoking prevalence declines over time. People ages 14-18 are at the highest risk to start smoking regardless of the birth cohort. People are more likely to quit at ages 20-30 and at the age of transition into retirement (60-65). Increased smoking cessation among young- and middle aged people is the major driver of decreasing smoker prevalence. The average smoking dose is lower for the recent birth cohorts. Women show more complex patterns of smoking behaviour than men.

Discussion and Conclusions: The obtained estimates of smoking behaviour can be used to optimize the current approach to smoking prevention and support further development of anti-smoking interventions that can be applied in clinical practice. Smoking prevention programs should target individuals of ages 14-18. Smoking cessation interventions should be optimised to reach smokers at ages 20-30 and those who are soon to retire.

Keywords: smoking histories, smoking prevalence, smoking cessation, smoking initiation, smoking intensity.

Introduction.

Although antismoking campaigns have reduced smoking prevalence in Germany from 36.9% to 29.2% over the 15-year period starting in 2000 [1], it is still considered to be high. Among smokers 16.3% of men and 8.8% of women consume more than 20 cigarettes per day, placing themselves in the category of heavy smokers [2]. Cigarette smoking leads to roughly 121,000 premature deaths per year [3] in Germany and is a major cause of many cardiovascular, severe respiratory, and oncological diseases [4] such as chronic obstructive pulmonary disease (COPD) and lung cancer.

Individual smoking exposure can be featured as age at smoking initiation, age at smoking cessation and smoking intensity, which is depicted by the average number of cigarettes smoked per day. Population level of smoking behaviour can be described through smoker prevalence, probabilities to initiate- and to quit smoking. Analysis of these parameters for specific ages and birth cohorts can support the development of optimal healthcare interventions directed to prevent or decrease the harmful consequences for the population. Studies which focus on these interventions benefit from the available data on the smoking history of individuals, difference in their age, gender and birth year [5, 6]. Such estimates have been generated for the USA [7], however, the smoking behaviour of Americans are not similar to the European people. Since 2000, for example, smoking prevalence in the US has been showing a steeper decline than in the Europe [1]. Due to the differences in the smoking behaviour, the estimates and their projections obtained for the US cannot be applied in studies, which focuses on the European populations without having biased inferences.

In this study, we produce the data which describe cohort-specific smoking patterns differentiated across genders and ages and represented by the prevalence of ever-, current-, and former smokers, smoking initiation and cessation probabilities, and smoking intensity indicated by the number of cigarettes smoked per day (CPD). The obtained data reflects the effects of the age groups and birth cohorts on smoking behaviour. Additionally, social forces and historical events can be gleaned from the obtained data.

Methods.

Data:

Data on smoking behaviour in Germany was obtained from three cross-sectional surveys conducted by the Robert Koch Institute (RKI) between 1997 and 2012: the German National Health Interview and Survey (GNHIES98) (1997-1999 with 7,124 participants), the German

Health Interview and Examination Survey for Adults (DEGS) (2008-2011 with 8,152 participants), and the German Health Update (GEDA) which engaged 21,262 (2009), 22,050 (2010) and 19,294 (2012) participants.

Statistical analysis:

Smoking initiation and cessation probabilities were estimated for each birth year (1920-1980) by a single year of age by fitting logistic regression models to the data from the surveys. We applied thin plate regression splines within the logistic models due to nonlinearity of smoking patterns. Smoking intensity was estimated as probabilities that fall into one of five ranges of CPD. The resultant estimates were used to determine the mean of smoking doses [7]. The prevalence of ever-, current- and former smokers were computed for each birth cohort (1920 -1980) using the estimates of the smoking initiation and cessation probabilities obtained from the regression analyses. All smoking parameters were projected up to the year 2025.

Detailed description of the datasets, the applied regression models and calculation of the prevalences is available in the online supplement.

Results.

Smoking initiation probability

The age- and birth cohort specific smoking initiation probabilities are illustrated on Figure 1 (left) by decennial birth cohort, age, and gender. Across all cohorts, a rapid increase in initiation probability is seen for ages 12–18, followed by a decrease after 19 up to 25 years of age. After the age of 35 the probability to start smoking is very low independent of the birth cohort. The probability to start smoking for men ranges from 11% to 15% being the highest between the ages of 16 and 18 years old regardless the birth year. For women the highest is in ages 17–18.

Smoking cessation probability

The curves of the statistically estimated probabilities of quitting smoking show cumulative conditional probability to stop smoking at a particular age, given that an individual was a smoker until that age (Figure 1, right). Although, the absolute number of people who quit smoking decreases starting at the age of 41, the cumulative probability to quit is continually increasing until it reaches maximum around age 62. After this age it continuously decreases with increasing age. A rapid increase of cessation probability is seen for ages between 20 and 30, particularly among women, and around the retiring age. Although, no decrease in initiation probability is observed in recent birth cohorts, cessation probability among them remarkably increases.

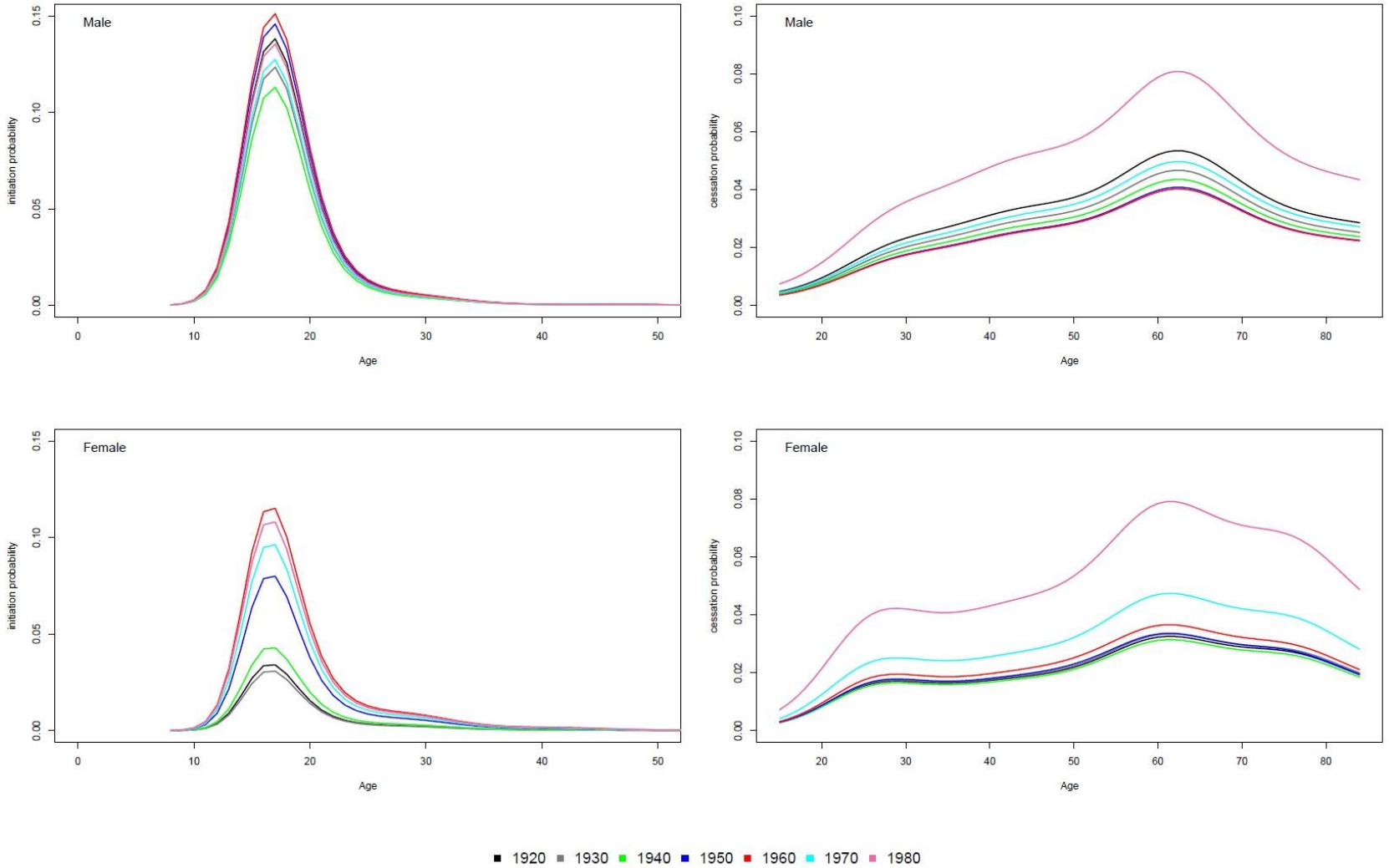


Figure 1. Age- and birth cohort-specific smoking initiation and cessation probabilities for men and women.

Prevalence

Figure 2 illustrates age- and birth cohort-specific percentage of people who ever smoked (both former- and current smokers). Majority of people start smoking between the ages of 15 and 20, however, a significant number begin to smoke earlier. The percentage of people who start smoking after the age of 35 is negligible. The prevalence of ever smoking females remains at a low level in the birth cohorts 1920-1940 and sharply increases in cohorts born after the end of the Second World War. Following a decrease in ever smoking female prevalence for the mid60s-mid70s birth cohorts, the percentage of women who ever smoked increases again in the recent birth cohorts. The prevalence of ever smoking males shows similar patterns across the birth cohorts, however, it is considerably higher for earlier cohorts and increases less rapidly later. The increase in prevalence in the most recent birth cohorts is less noticeable. Therefore, one can see that the ever smoking female prevalence approaches the male prevalence.

The former smoker prevalence tends to increase with age for all birth cohorts and is at its highest level in the most recent birth cohorts (Figure 2). The age-specific proportion of former smokers in ever smoker prevalence in women is relatively constant until the late 50s birth cohorts (Figure 3). From the early 60s birth cohorts the ratio increases for all ages due to high smoking cessation probability among young- and middle aged people from the recent cohorts. The age-specific ratios for men display a similar but less emphasized trend. Current smoking prevalence peaks occur for the ages around 20-25 years across all cohorts and regardless of gender (Figure 4). It reaches the highest point for the 1960 birth cohort and then decreases over time when moving towards the recent birth cohorts. An increase in smoking initiation for the late 70s cohorts is not visible in the current smoking prevalence due to an increase in the quitting probability in the young smoking population.

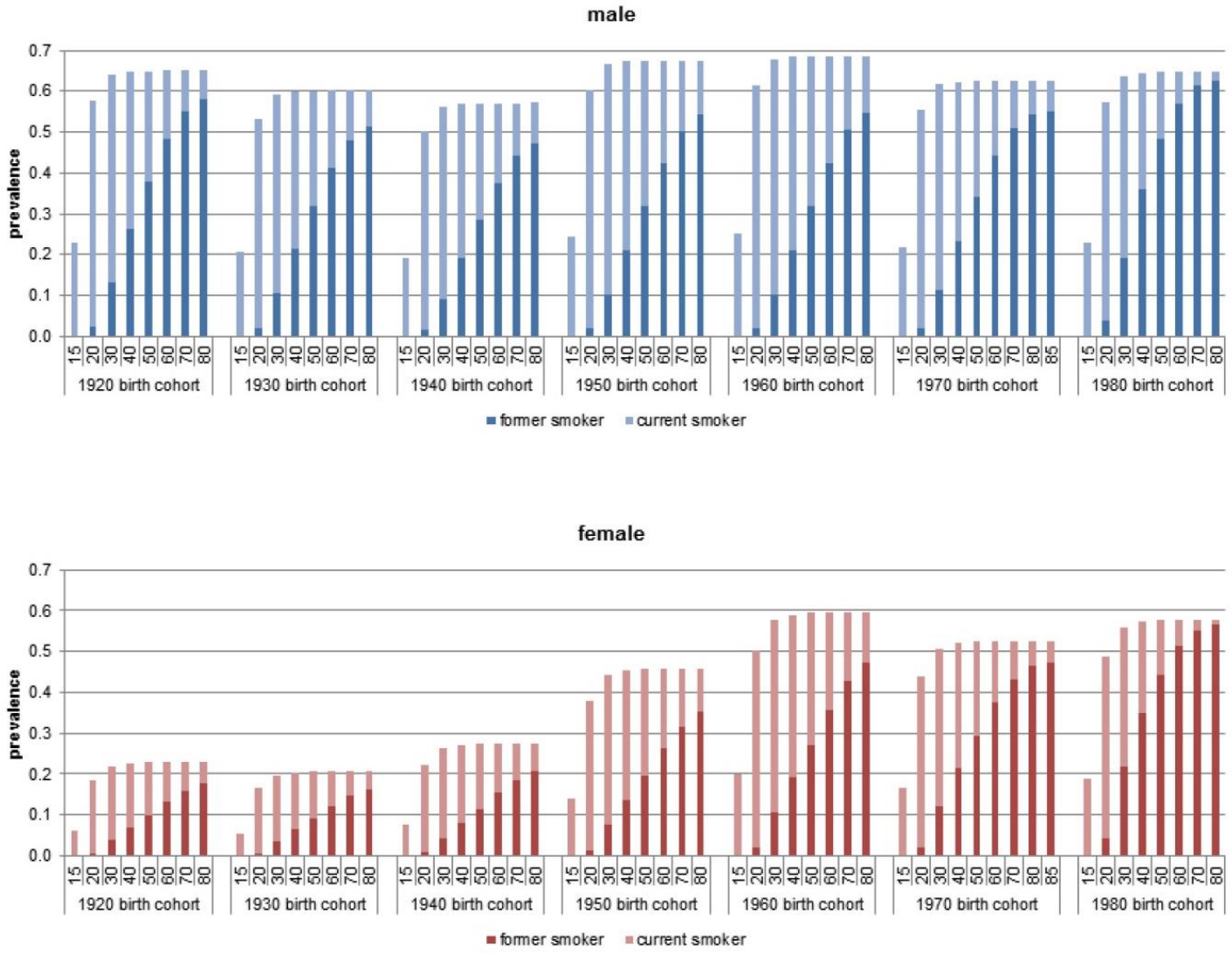


Figure 2. Age- and birth cohort-specific smoking initiation and cessation probabilities for men and women.

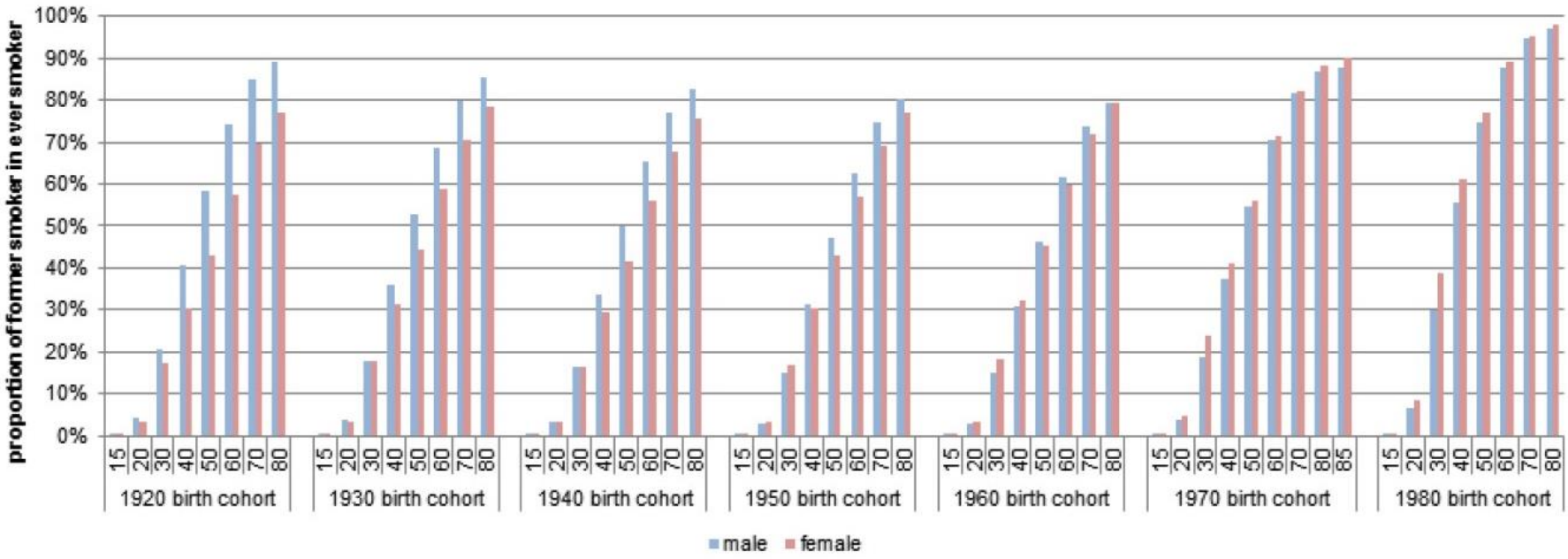


Figure 3. Age- and birth cohort-specific proportions of former smokers in ever smoker prevalence for men and women.

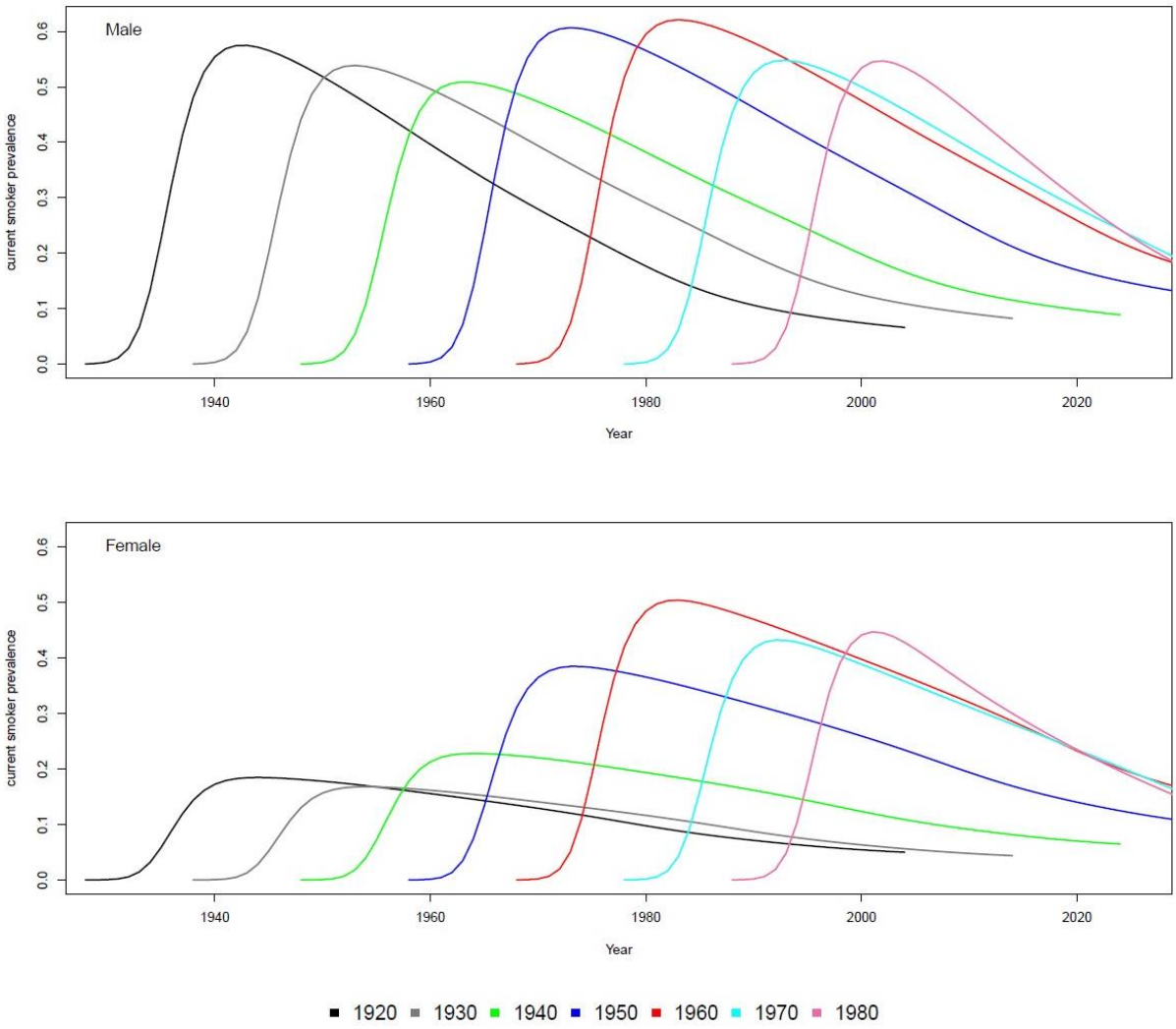


Figure 5. Age- and birth cohort-specific smoking intensity given in average number of cigarettes smoked per day for men and women.

Smoking intensity

Figure 5 illustrates the distribution of the average number of cigarettes smoked per day by age for decennial one-year birth cohorts of men and women. Overall, the numbers for women are lower than those for men. For both genders, the mean of CPD reaches its maximum at ages 40–45 and steadily declines during the later ages. The curves for men show a sharper decline. The mean number of cigarettes smoked per day remains below 25 for men and below 20 for women across birth cohorts. With time, smoking intensity tends to fall, with its peak in birth cohorts of 1950–1965.

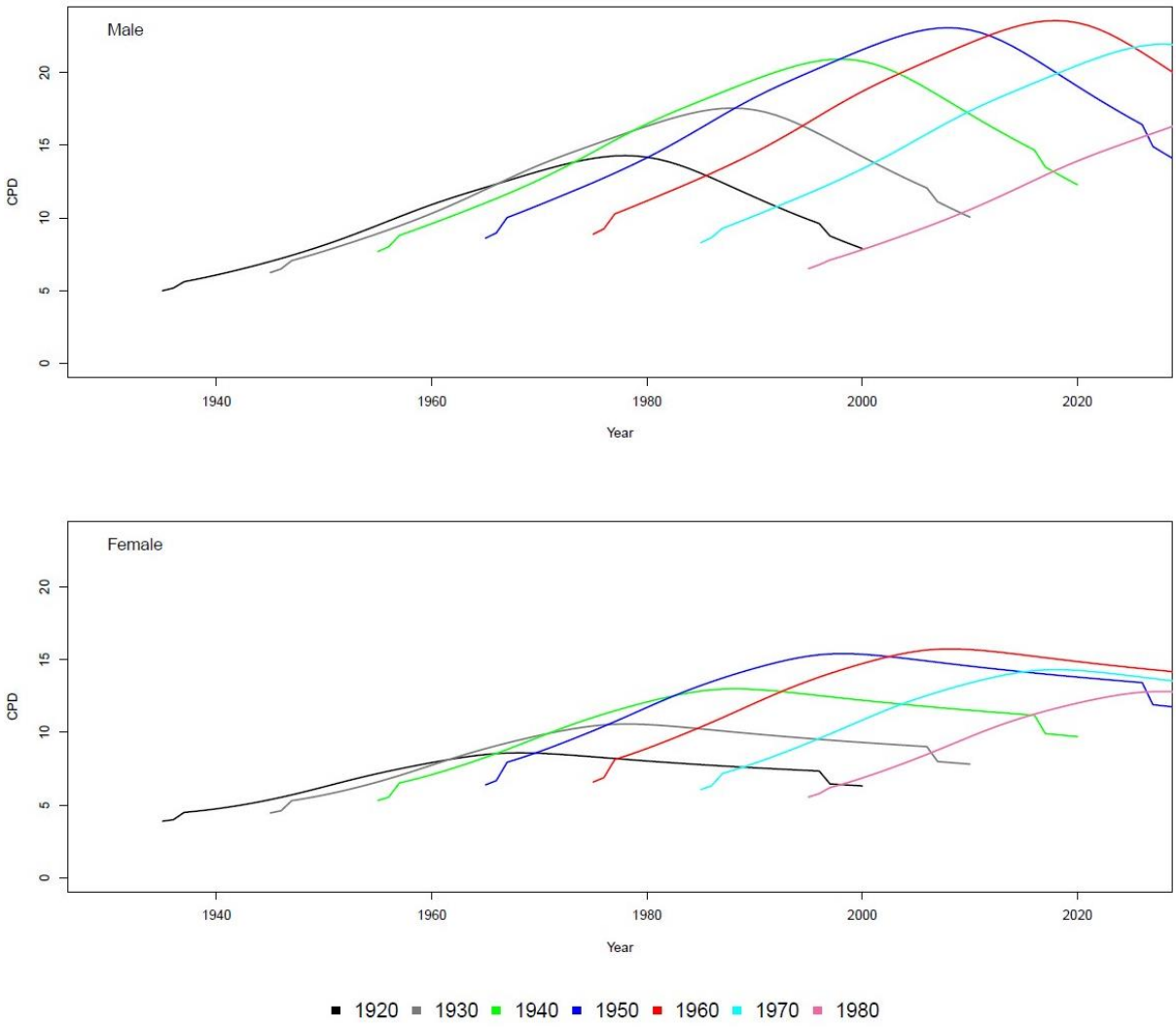


Figure 5. Age- and birth cohort-specific smoking intensity given in average number of cigarettes smoked per day (CPD) for men and women.

Discussion.

The present study statistically estimates the major age- and birth cohort-specific parameters of smoking histories for the German population. Using the obtained estimates one can analyze temporal patterns of the smoking behaviour for young- and old-, male- and female smokers of different birth cohorts. The results can help to understand the trends observed in the cross-sectional data.

For the considered birth cohorts, the age-specific estimates of the current smoking prevalence shows that the percentage of the population who currently smoke decreases with an increasing age starting with age of around 25 years. The respective birth cohort-specific estimates represent temporal patterns and show a decrease in the prevalence over time when moving towards the recent years. These differences are governed by the age- and the birth cohort-specific

smoking initiation and cessation probabilities. Examination of the curves for the smoking initiation probability and the ever smoker prevalence allows for the conclusion that there are no temporal trends in the age of the highest smoking initiation probability, so that, people between ages 14 and 18 years are at the highest risk to begin smoking regardless of the birth year. At this age an individual reaches the peak of puberty and tends to seek autonomy. People at this age are considered to be the most susceptible to be influenced by friends and social environment [8]. Unfavorable social environment can play a central role in inducing smoking among individuals at middle of adolescence.

Smokers of the recent birth cohorts have a considerably higher probability to quit after the age of around 20 years than those of the older cohorts. It is illustrated by a steeper slope of the curves for the younger cohorts (starting with 1980) for ages between 20 and 30 years. As long as the smoking initiation probability does not show a constant decrease over time, the increased smoking cessation probability majorly contributes to the decline of current smoking prevalence. The effects of tobacco control measures implemented in Germany can be gleaned from these patterns. The tobacco control included an approximately 42.5% tobacco tax raise [9], restrictions on tobacco commercials, a ban on the smoking in public places and the minimum age of legal cigarette consumption [10–12] . According to the Deutsches Krebsforschungszentrum (German Cancer Research Center), these measures led to an approximately 34% decrease in cigarette consumption during 2002–2005 [9]. The increase in the smoking cessation probability may be caused by the reduction of peer group effect resultant from implementation of the tobacco control. This hypothesis can be supported by a study from the USA which concludes that introducing clean indoor air laws led to a spread of voluntary smoke-free-home policies [13]. Additional reasons for the comparatively easy smoking cessation in the recent cohorts can be the reduction of the addiction level resultant from a decrease in the smoking intensity in these cohorts [14]. A rapid increase in the smoking cessation probability is seen for ages characterized as approaching parenthood and retirement. A study by Lang et al suggests that individuals who go through the transition into retirement are more likely to quit smoking than those who do not [15].

In our resultant data, women show more complex smoking patterns compared to men. In the related literature, gender patterns of smoking behaviour in a historical context have been extensively examined [16–18]. From the 19th century to the beginning of the 20th century, tobacco consumption was mainly a male habit [16, 19]. During the Second World War, the well-established tobacco consumption among men continued to increase [19]. These tendencies are reflected in our estimates of the initiation probability and current smoker prevalence for female cohorts born in the first half of the 20th century, which are significantly lower than their male counterparts. During the later period of the 20th century, the imagery surrounding cigarette

smoking changed through advertising campaigns targeting women. The consequent rise in tobacco consumption among women is represented in our estimates by the increase in female smoking prevalence in the period after the war. After the reunification of Germany in 1990, the smoking prevalence in women from East Germany has been reported to increase significantly, while in the Western part of Germany the smoking prevalence among women decreased [20]. In turn, for the male population the reunification is reported to not bring considerable changes in the smoking prevalence [20].

Currently, the female smoking prevalence represented by younger cohorts in our estimates tends to reach the male smoking prevalence. These results correspond to the results obtained from the Micro Census data [21] . The curves for the probability of quitting smoking for women reflect quitting tendencies at the age of becoming a mother for the first time. According to the German birth tables, the mean age of giving birth to a first child was 26.6 in 1960 and 30.9 in 2014 [22] . The patterns for men show flatter curves for these ages.

The resultant estimates are subject to certain limitations of the applied data. The surveys are cross-sectional but not longitudinal studies, meaning that the interviewed individuals have not been observed over time and the smoking parameters are estimated based on individual smoking histories recorded at the time of the survey. The estimations for the cohorts born before 1935 might be biased because of a limited number of observations for them in the datasets. Additionally, it was assumed that cessation age does not depend on the initiation age and smoking intensity. Due to the cross-sectional nature of the data, the average number of cigarettes smoked per day was recorded on the date of the interview and taken to be constant for the period of smoking. Despite these limitations, our study provides estimates of smoking histories by single years of age (8–84) and birth cohorts (1920–1980) and current and former smoker prevalence over time. The obtained estimates capture population dynamics of exposure to cigarette smoking over time, as opposed to simply representing the point prevalence obtained from the surveys [7]. The fields of application include topics in medical and public health research of smoking-related issues such as the modelling of smoking-induced diseases (e.g., lung cancer, COPD), health economic evaluations (e.g., lung cancer screening), and evaluations of the effects of different political measures on smoking behaviour. The results suggest that interventions should be developed to specifically target prevention of smoking initiation among people at the age of 14-18 and promote smoking cessation among those who are soon to retire and individuals of ages 20-25 years old, particularly young women. Interventions such as the tobacco-counselling steps [23] could be optimized for the target group and incorporated into clinical practice in order to prevent high risk individuals to begin smoking as well as to help current smokers quit smoking.

References

1. WHO: Global report on trends in prevalence of tobacco smoking 2015.
2. Eurostat: Tobacco consumption statistics. http://ec.europa.eu/eurostat/statistics-explained/index.php/Tobacco_consumption_statistics#Online_publications (last accessed on 18 April 2016).
3. Pötschke-Langer M, Kahnert S, Schaller K, et al. (eds.): Tabakatlas Deutschland 2015 (Tranlation: Tobacco Atlas Germany 2015). 1st ed. Heidelberg 2015.
4. Gibson GJ, Loddenkemper R, Sibille Y, Lundback B: The European Lung White Book: Respiratory Health and Disease in Europe. 2nd ed. Sheffield: European Respiratory Society 2013.
5. Moyer VA: Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160(5): 330–8.
6. Koning HJ de, Meza R, Plevritis SK, et al.: Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med 2014; 160(5): 311–20.
7. Holford TR, Levy DT, McKay LA, et al.: Patterns of Birth Cohort–Specific Smoking Histories, 1965–2009. American Journal of Preventive Medicine 2014; 46(2): e31-e37.
8. Park S-H: Smoking and adolescent health. Korean J Pediatr 2011; 54(10): 401–4.
9. Deutsches Krebsforschungszentrum (ed.): Tabaksteuererhöhungen und Rauchverhalten in Deutschland: Aus der Wissenschaft – für die Politik. Heidelberg 2014.
10. Kröger C, Mons U, Klärs G, Orth B, Maschewsky-Schneider U, Lampert T: Evaluation des Gesundheitsziels „Tabakkonsum reduzieren“ (Translation: Evaluation of the health target “tobacco control). Bundesgesundheitsbl. 2010; 53(2): 91–102.
11. Deutsches Krebsforschungszentrum: Perspektiven für Deutschland: Das Rahmenübereinkommen der WHO zur Eindämmung des Tabakgebrauchs. Heidelberg 2011.
12. Forum Gesundheitsziele Deutschland: Nationales Gesundheitsziel „Tabakkonsum reduzieren": gesundheitsziele.de: Kooperationsverbund zur Weiterentwicklung des nationalen Gesundheitszieleprozesses. www.gesunheitsziele.de.
13. Cheng K-W, Glantz SA, Lightwood JM: Association between smokefree laws and voluntary smokefree-home rules. American Journal of Preventive Medicine 2011; 41(6): 566–72.

14. Messer K, Trinidad DR, Al-Delaimy WK, Pierce JP: Smoking cessation rates in the United States: a comparison of young adult and older smokers. Am J Public Health 2008; 98(2): 317–22.

15. Lang IA, Rice NE, Wallace RB, Guralnik JM, Melzer D: Smoking cessation and transition into retirement: analyses from the English Longitudinal Study of Ageing. Age Ageing 2007; 36(6): 638–43.

16. Elliot R: Destructive but Sweet: Cigarette Smoking among Women 1890-1990. Glasgow University, Glasgow.

17. Jacobson B: Beating the Ladykillers - Why Women Smoke. London: Gollancz.

18. Jacobson B: The Ladykillers - why Smoking is a Feminist Issue. London: Pluto Press 1981.

19. Hunt K: Contextualizing smoking: masculinity, femininity and class differences in smoking in men and women from three generations in the west of Scotland. Health Education Research 2004; 19(3): 239–49.

20. Vogt T, van Raalte A, Grigoriev P, Myrskylä M: German East-West Mortality Difference: Two Cross-Overs Driven by Smoking. Working Paper. http://www.demogr.mpg.de (last accessed on 12 January 2017).

21. Statistisches Bundesamt: Microcensus - questions about the health. http://www.destatis.de (last accessed on 16 August 2016).

22. Eurostat: Mean age of women at childbirth: http://ec.europa.eu/eurostat/tgm/table.do?tab=table&plugin=1&language=en&pcode=tps00017
. http://ec.europa.eu/geninfo/legal_notices_en.htm (last accessed on 24 August 2016).

23. Cosci F, Pistelli F, Lazzarini N, Carrozzi L: Nicotine dependence and psychological distress: outcomes and clinical implications in smoking cessation. Psychol Res Behav Manag 2011; 4: 119–28.

Supplement:

Data description:

Data on smoking behaviour in Germany were obtained from three cross-sectional surveys conducted by the Robert Koch Institute (RKI) between 1997 and 2012: the German National Health Interview and Survey (GNHIES98) (1997-1999 with 7,124 participants), the German Health Interview and Examination Survey for Adults (DEGS) (2008-2011 with 8,152 participants), and the German Health Update (GEDA) which engaged 21,262 (2009), 22,050 (2010) and 19,294 (2012) participants. We chose these surveys because they provided a large pooled sample size of 77,882 respondents and contained all the variables of interest to our analysis: smoking status at the interview date, age at starting and quitting smoking, form of smoking, and the number of cigarettes smoked per day. In our analysis we focused on the smoking of boxed and hand-rolled cigarettes which constitute the major means of daily tobacco consumption in Europe[12]. Alternative large surveys (Micro Census [13], the German Socio-Economic Panel (SOEP) [14], German Epidemiological Survey of Substance Abuse (ESA)) [15] provided insufficient information for our analyses.

For the estimation of the smoking parameters, datasets from GEDA and DEGS were combined into a single data set (DEGS/GEDA). GNHIES98 and DEGS/GEDA applied different weights to the observations; therefore, we did not combine all three of them into one single data set. Instead, we examined GNHIES98 and DEGS/GEDA separately. We performed a statistical analysis using data from each dataset with the application of the respective weights and then the resultant estimates were aggregated based on the proportions of weighted observations for a single birth year.

The German National Health Interview and Survey (GNHIES98), was administered from 1997 to 1999 [11]. A total of 7, 124 individuals between 18 and 79 years of age participated in this survey. All participants were asked to fill out a questionnaire; additionally, some subgroups were invited to give more details on different topics related to smoking.

The second survey, the German Health Interview and Examination Survey for Adults (DEGS), took place from 2008 to 2011 and involved 8,152 people between the ages of 18 and 79 [12]. This study collected a wide range of data on health and lifestyle employing standardized computer-assisted personal interviews, self-administered questionnaires, standardized measurements, and tests.

The third survey, the German Health Update (GEDA), was conducted in 2009, 2010, and 2012 and included 21,262 (2009), 22,050 (2010) and 19,294 (2012) participants of 18–86 years of age respectively [13]. Computer-aided telephone interviews were used.

Statistical analysis:

The surveys contained a restricted range of survey years which limited the ability to estimate period effects, therefore, the period was excluded from the analysis, and the age and cohort were the only temporal components affecting smoking history.

Estimating smoking initiation probability:

We estimated the smoking initiation probability for each dataset and gender using a single year of age and one-year birth cohort. We constructed a binary variable with two possible values: 1 if the *i*-th individual (cohort,c) started to smoke at age a and 0 otherwise. The probability of the outcome was determined as a function of age and cohort:

$$\text{logit}\{p(a,c)\} = \beta_0 + \beta_a(a) + \beta_c(c),$$

where $p(a,c)$ is the probability of smoking initiation, β_0 is an intercept, and $\beta_{\cdot}(\cdot)$ is given by a thin plate regression spline. For each cohort represented in each dataset, we defined individuals who started smoking at age$a$ and who had never smoked up to that age [9]. The data comprise datasets which were used for fitting the logistic model. The cohort effect,β_c, was assumed to remain constant for the cohorts born after 1982. Using the resultant coefficients, the estimates of smoking initiation probability were projected to the year 2025 for ages 15–76.

Estimating smoking cessation probability:

Smoking cessation was characterized as having quit smoking and having not smoked for at least two years before the interview.

For the estimation of smoking cessation probabilities, we followed the respondents of each year of age starting with the age at smoking initiation through the age at smoking cessation. Using this data, we determined the smokers who quit and smokers who continued to smoke at the given age and the year of birth. The data was then used to fit an additive logistic model in order to obtain the conditional probabilities of quitting:

$$\text{logit}\{q(a,c)\} = \beta_0 + \beta_a(a) + \beta_c(c),$$

where $q(a,c)$ is the probability of quitting smoking, β_0 is an intercept, and $\beta_{\cdot}(\cdot)$ is given by a thin plate regression spline. Using this regression, we obtained the estimates of the conditional probability of quitting at a particular age, given the subject was a smoker. Based on the results of the regression, the estimates were projected to the year 2025 for ages 15–84. Fitting was performed in R using the GAM function.

Estimating prevalence of ever-, current-, former smokers:

To estimate the prevalence of current and former smokers for each dataset and gender, we used the estimated probabilities for smoking initiation and cessation. Therefore, following Holford et. al., we calculated the proportion of subjects who had ever been smokers, P_E and the cumulative proportion of smokers who had not quit smoking, Q [10]:

$$P_E(a,c) = 1 - \prod_{i=1}^{a}[1 - p(i,c)]$$

$$Q(a,c) = \prod_{i=15}^{a}[1 - q(i,c)] \text{ with } q(a,c) = 0 if a < 15$$

The respective prevalence was then defined by the following equations [10]:

$$P_C(a,c) = P_E(a,c)Q(a,c)$$

$$P_F(a,c) = P_E(a,c) - P_C(a,c)\ ,$$

where P_C is the prevalence of current smokers and P_F is prevalence of former smokers.

Estimating smoking intensity:

Both datasets contained records on the average number of cigarettes smoked per day (CPD), which were used to analyze smoking intensity. In order to include smoking intensity, we constructed an ordered categorical outcome variable and defined the following intervals of CPD with the centre of the intervals given in brackets: CPD≤5 (3); 5< CPD≤15 (10); 15<CPD≤25 (20); 25<CPD≤35 (30); 35<CPD≤45 (40); and 45<CPD (60) [9].

The outcome variable was regressed against age and cohort using a cumulative logistic model and thin plane regression splines. The model was fitted to the data from the two datasets for

each gender separately. The fitted estimates represented the probabilities of each cohort aged 15–76 falling into each category of smoking intensity. The resultant estimates were used to determine the mean smoking dose [9], and were also projected to 2025.

Validation.

In order to validate our findings with the studies, which determine smoking prevalence in Germany, we accumulated the estimates over the birth-cohorts and ages. Our findings on prevalence and cigarette smoking intensity conform to the statistics given in the WHO report (WHO)[4] for Germany and those obtained by Kraus et al. (Kraus, L., Pabst, A., Gomes de Matos, E., Piontek, D. 2014)[17]. The WHO reports its estimates and projections of current smokers' prevalence (over 15 years old) in Germany for 2000–2025. Our results not only align with the estimates of WHO, the generated estimates add essential age and birth cohort–specific details.

Table 1 summarizes the estimates given by WHO and those obtained in this study for that period.

Table 1: Comparison of the study results with the results reported by WHO: prevalence of current smokers over 14 years of age.

Year	**WHO [4]: Current Tobacco-Smoking Men (%)**	**Treskova et al. Current Tobacco-Smoking Men (%)**	**WHO[4]: Current Tobacco-Smoking Women (%)**	**Treskova et al. Current Tobacco-Smoking Women (%)**
2000	36.9	36.2	26.5	25.7
2005	34.0	34.7	25.5	25.6
2010	31.6	33.0	24.4	25.0
2015	29.3	31.3	23.3	24.0

FIGURE 1: EVER SMOKER PREVALENCE

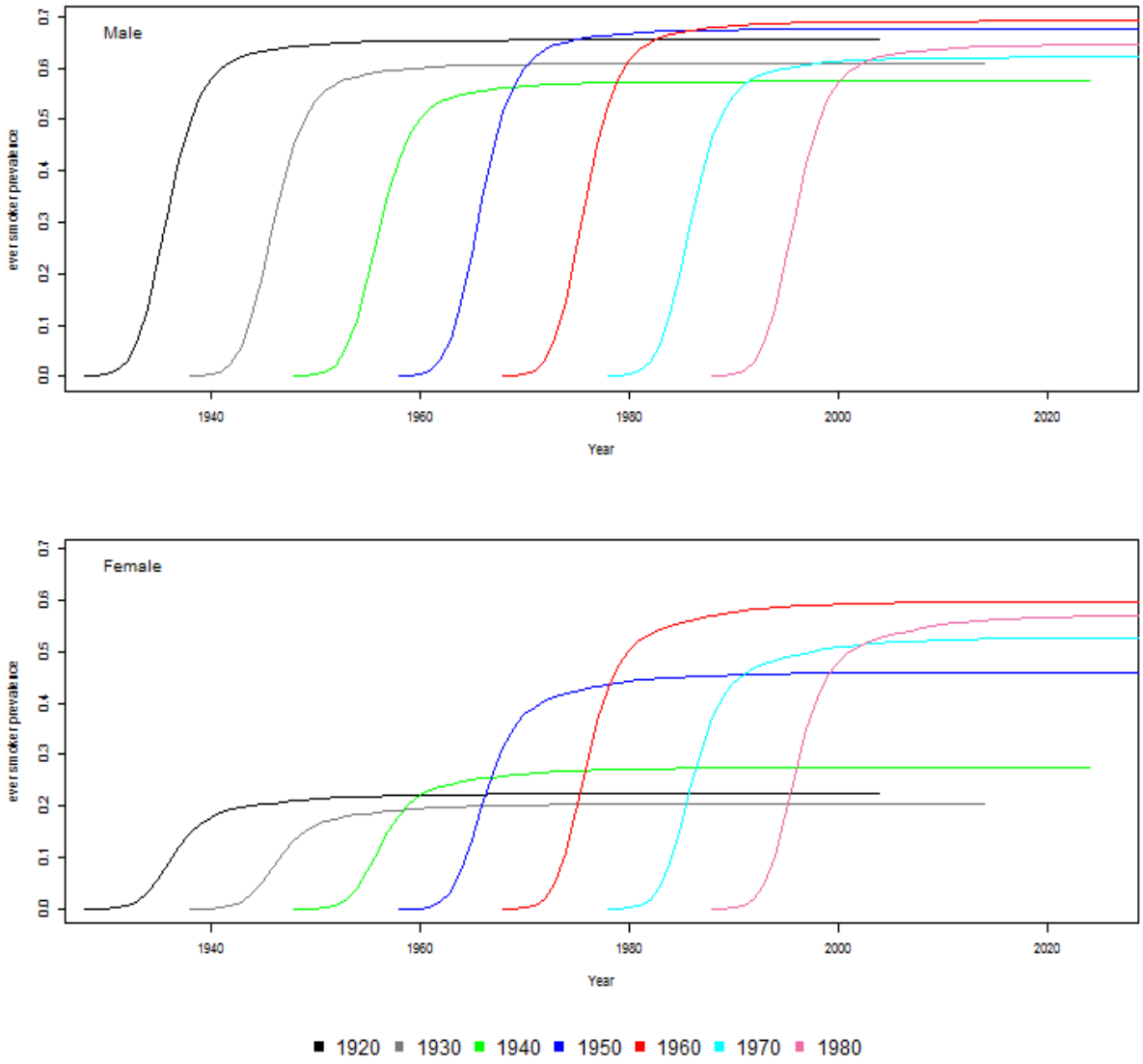
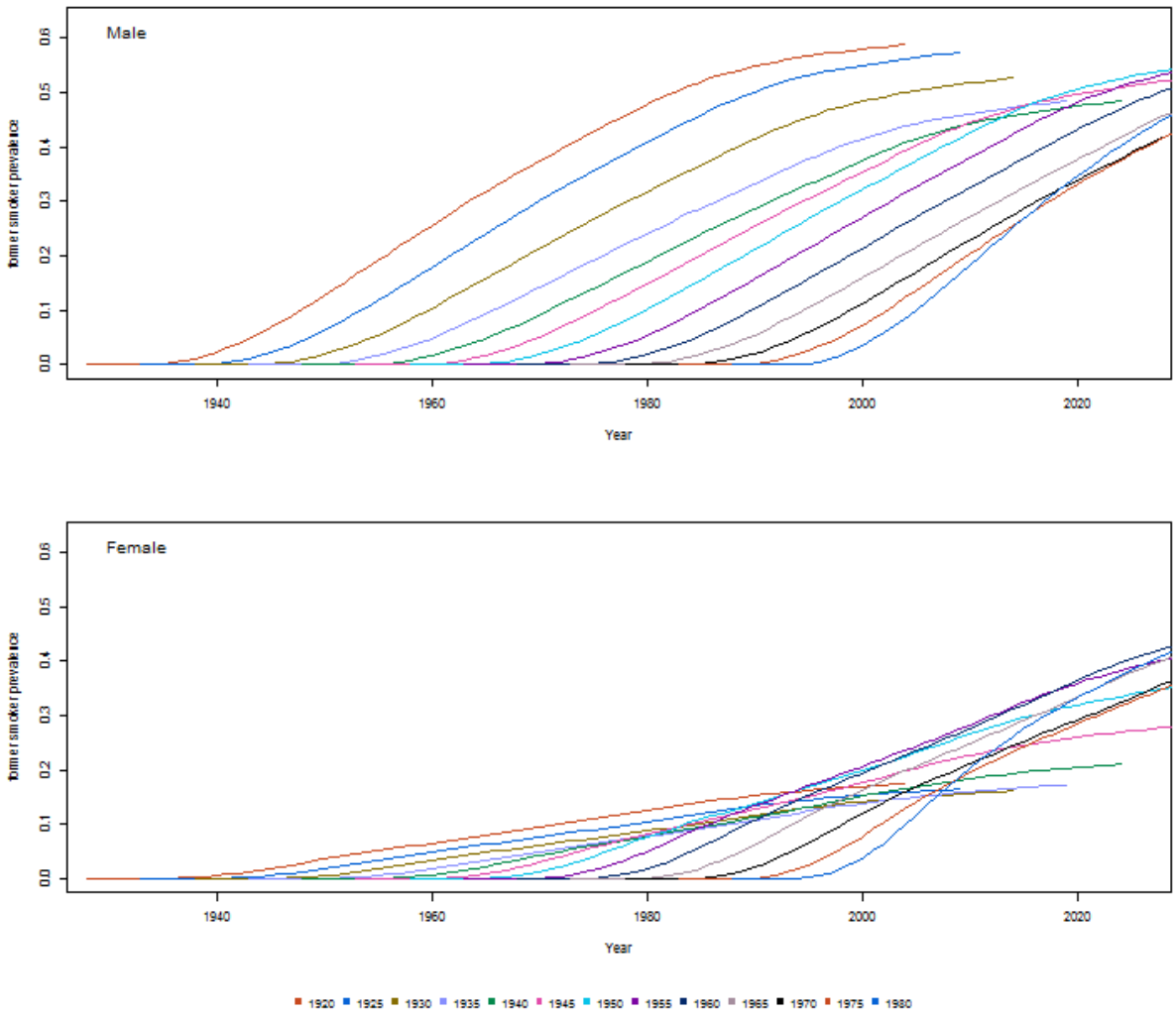


FIGURE 2: FORMER SMOKER PREVALENCE



Article 2

Analysis of driving factors of willingness to use and willingness to pay for existing pharmacological smoking cessation aids among young and middle-aged adults in Germany

Aumann I, Treskova M, Hagemann N, Graf von der Schulenburg J-M

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ORIGINAL RESEARCH ARTICLE

Analysis of Driving Factors of Willingness to Use and Willingness to Pay for Existing Pharmacological Smoking Cessation Aids Among Young and Middle-Aged Adults in Germany

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Abstract

Background Smoking cessation is a challenging task with a high risk of relapse. Depending on the choice of medication and duration of therapy, the costs of using a smoking cessation aid can be high. Additionally, these costs are not covered by health insurance in Germany. Information on willingness to use (WTU) and willingness to pay (WTP) for smoking cessation aids is valuable for developing different smoking cessation strategies.

Objectives The study analyses WTU and WTP for three pharmacological smoking cessation aids (nicotine replacement therapy (NRT), bupropion and varenicline) among young and middle-aged adults in Germany and attempts to determine their major driving factors.

Methods Two cross-sectional internet-based surveys of smokers over 18 years of age were conducted in 2014 and 2015 in Germany. Respondents were asked about smoking-related issues and WTU and WTP for each therapy. The contingent valuation method with payment cards was used to measure WTP. Descriptive statistics, logistical regression and accelerated failure-time regression models were performed.

Results The total sample size is 505. Half of the respondents are willing to use NRT and one-third are willing to use bupropion and/or varenicline. WTU induces positive WTP; however, the magnitude of WTP is beneath the market price. WTU significantly increases with a higher addiction level and if smokers have previously heard about the therapy.

Conclusion This study indicates different points to be considered for policy development. Promotion information and improving awareness about medication aids might increase WTU, and development of monetary incentives for young smokers could create a better chance for successful smoking cessation.

Key Points for Decision Makers

Pharmacological smoking cessation methods should be directed to smokers with strong addiction.

People who are familiar with NRT therapy are likely to be willing to use and pay for it. Promotion information and improving awareness about medication aids and their efficacy might increase willingness to use them.

Willingness to pay for pharmaceutical smoking cessation aids is below the market price for all therapy options; therefore, different strategies, e.g. reducing the price of medications or development of co-payment options or bonus payments by health insurance companies under the condition of successful quitting, should be discussed.

Electronic supplementary material The online version of this article (doi:10.1007/s40258-016-0239-0) contains supplementary material, which is available to authorized users.

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1 Introduction

Smoking is one of the main contributing factors to leading causes of death such as chronic obstructive pulmonary disease, lung cancer and cardiovascular diseases. According to the World Health Organization (WHO), smoking-related conditions are responsible for six million deaths annually [1]. In Germany, smokers account for 26 % of the population, a percentage similar to the smoking prevalence in Europe (28 %). Most of the current smokers are young and middle-aged adults. The smoking rate for these groups is higher than the population-level prevalence: approximately 29 % for young adults (aged 15–24 years) and 37 % for people aged 35–39 years [2]. The WHO also reports that more than half of the smokers in Europe are interested in quitting smoking [3]. According to statistics, over the last year, 21 % of European smokers have tried to quit smoking and the overall percentage of people in Europe who have attempted to stop smoking has reached 63 %.

Owing to the physically and mentally addictive nature of smoking, quitting is a considerable challenge, with a high risk of relapse. To support quitting smoking, various measures are available: psychological counselling (face-to-face or via telephone), self-help measures (books, applications and websites), individual or group therapy, and alternative methods such as acupuncture. Additionally, nicotine replacement therapy (NRT), bupropion and varenicline have been found to be effective in supporting smoking cessation [4]. However, in Germany, the cost of these medications is borne by the user, whereas other interventions targeting smoking behaviour are either free of charge or covered by health insurance programs.

Evidence-based clinical practice guidelines for tobacco cessation recommend a combination of pharmacotherapy, physician counselling and social support as a key strategy for smoking cessation [5]. Although usage of medications is included in the recommendations, smokers generally do not use pharmacotherapy. A recent smoking cessation trial in Germany reported that only 1 % of smokers have used prescription drugs like varenicline and bupropion [2]. Information about the number of persons who have used NRT is not available.

Several studies have analysed the cost-effectiveness of pharmacological therapies for smoking cessation; however, the authors point out the need to define a threshold at which a therapy is considered to be cost-effective [6]. Among the several factors that predetermine the choice of a cost-effectiveness threshold is the amount of money that people are willing to spend to gain the benefits of the intervention. Five studies have analysed willingness to pay (WTP) for different pharmacological smoking cessation therapies in different countries [7–11]. Most of these studies focus on WTP in hypothetical scenarios such as the development of a new effective medication [7] or a smoking cessation therapy that gives a guarantee for stopping smoking [8].

In Germany, WTP for smoking cessation medication has not yet been investigated. Most of the smokers in Germany are young adults and the German health insurance companies do not reimburse pharmacological smoking cessation therapies, so people must bear the costs of these medications themselves. In these settings, estimation of WTP and investigation of its driving factors might be useful for developing public health programs that target smoking cessation.

In this study, we investigate willingness to use (WTU) and WTP for smoking cessation therapy in young and middle-aged adults in Germany. We focus on three medications which have been approved in Germany as smoking cessation aids: NRT, bupropion and varenicline. NRT is an over-the-counter (OTC) medicine; it exists in different forms such as patches, gum, lozenges, inhalers and nasal sprays [12]. In contrast to NRT, bupropion and varenicline are available only on prescription and are sold in the form of pills. Although all the substances serve to reduce nicotine cravings, they differ in efficacy, drug delivery form, side effects and price. We examine the effects of demographical, socioeconomic and smoking-related characteristics on WTU and WTP for each therapy. In our analysis, we aim to inform development of smoking cessation policies among young people.

2 Methods

2.1 Study Type and Dataset

Two cross-sectional Internet-based studies were conducted in Germany over two periods: between May and August 2014 and between May and June 2015. The major criteria for enrolment in the survey were being a current smoker and age between 18 and 65 years. People who were undergoing a smoking cessation program were excluded from the survey. Participants were recruited actively via mail and passively via social networks, several smoking forums and self-help groups. No incentive was offered for participation in the survey. The study was approved by the Committee for Clinical Ethics of the Hanover Medical School.

2.2 Questionnaire

In order to examine WTU and WTP for the three therapies, we developed a questionnaire which included sections on demographic and socioeconomic characteristics and

smoking habit issues (see Supplemental Material, Appendix A). It also included questions regarding experience with smoking cessation therapies as well as WTU and WTP for each of the three drugs.

In the first part, respondents were asked questions related to their smoking history and nicotine dependency. Smoking addiction was measured using the Fagerström test [13]. Additionally, participants were asked about the age at which they began smoking, the number of smokers in their social environment (peer group) and whether they wish to quit smoking.

The second part of the questionnaire focused on the pharmacological treatment options and questions about WTU and WTP. To inform respondents about the therapy options, a description of each therapy was provided: Characteristics of the nicotine patches, administration of bupropion or varenicline, and information about intake, dosages, odds of success and potential side effects. Treatment effectiveness rates were based on the mean values obtained from different studies [12, 14]. In the following sequence of therapy-related questions, respondents were asked (1) whether they had heard about the therapy and had experience using the indicated medication; (2) based on the provided information about the therapy, whether they would be willing to use it if it is free of charge; (3) and regardless of the response to the WTU question, whether they would be willing to pay for the medication aid. By including the yes-no question on WTP for all respondents, we sought to prevent misunderstanding. Those who stated 'no' when asked about WTU and 'yes' when asked about WTP were excluded from further analysis.

To measure WTP, the contingent valuation method with payment cards was used. Contingent valuation usually involves asking individuals directly in a survey about the maximum amount of money they are willing to pay to gain the commodity in question [15–18]. In our survey, respondents were first asked whether they are willing to pay for the therapy, and those who chose 'yes' were asked to choose a range of values within which they are ready to spend for the related therapy. The range of values has been defined according to results from prior interviews with smokers. We asked this group which value ranges they would find understandable and preferable. The common answer was 10-Euro intervals, and the usual reason was that €10 was the amount of money they usually paid for nearly two cigarette packages. Ten-Euro intervals were constructed ascending and descending from a middle interval which included the current market price of the product under consideration. We also constructed the lowest interval as less than a certain amount without giving a certain low boundary in order not to lose information, particularly answers from people who would have omitted choosing an interval if they had not found a proper category.

Figure 1 illustrates this process, showing questions that lead to possible response options for WTP. The example is given for NRT and is similar for other therapies, but the WTP intervals were adjusted for each medication. At the end of the questionnaire, respondents were asked to provide information on characteristics such as age, sex, education, current employment status, income and insurance status.

2.3 Statistical Analyses

Descriptive statistics were calculated separately for each therapy for the outcome and predictor variables. Determinants of WTU and WTP were assessed for each medication separately using regression methods based on distributional characteristics of the outcomes (see equations in Supplemental Material, Appendix B). According to the design of the questionnaire, the outcomes consisted of three variables of interest for each therapy: (1) WTU, which had two possible values termed 'yes' and 'no'; (2) WTP, which also had two possible values termed 'yes' and 'no'; (3) and ordered WTP, shown as 10-Euro intervals. Only respondents who stated 'yes' when asked if they are willing to pay were asked to choose one of the intervals in accordance with their preferred amount. Therefore, a point value of WTP is uncertain; however, it falls within a particular interval. When interval-censoring occurs, survival analysis can be applied by exchanging a failure time for WTP [19–21]. Although accelerated failure-time models are not conventional for WTP studies, they allow an analysis of WTP interval bids as dependent variables and have been considered appropriate for dealing with WTP intervals in previous studies [21–25]. In our study, distribution of upper and lower values of the resultant intervals was better approximated by a Weibull distribution. Therefore, for the regression analysis of the ordered WTP, we used accelerated failure-time models with a Weibull distribution.

For the dichotomous outcomes of WTP and WTU, we applied logit regressions, which are conventional for this type of outcome.

Predictors were chosen in accordance with the related literature, research hypotheses and a backward variable selection procedure. They included age, gender, income, employment, presence of health restrictions due to smoking, willingness to quit smoking, attempts to quit smoking, addiction degree, peer group, having heard about the therapy and experience with usage of related therapy.

All regression analyses were performed using the statistical software R.

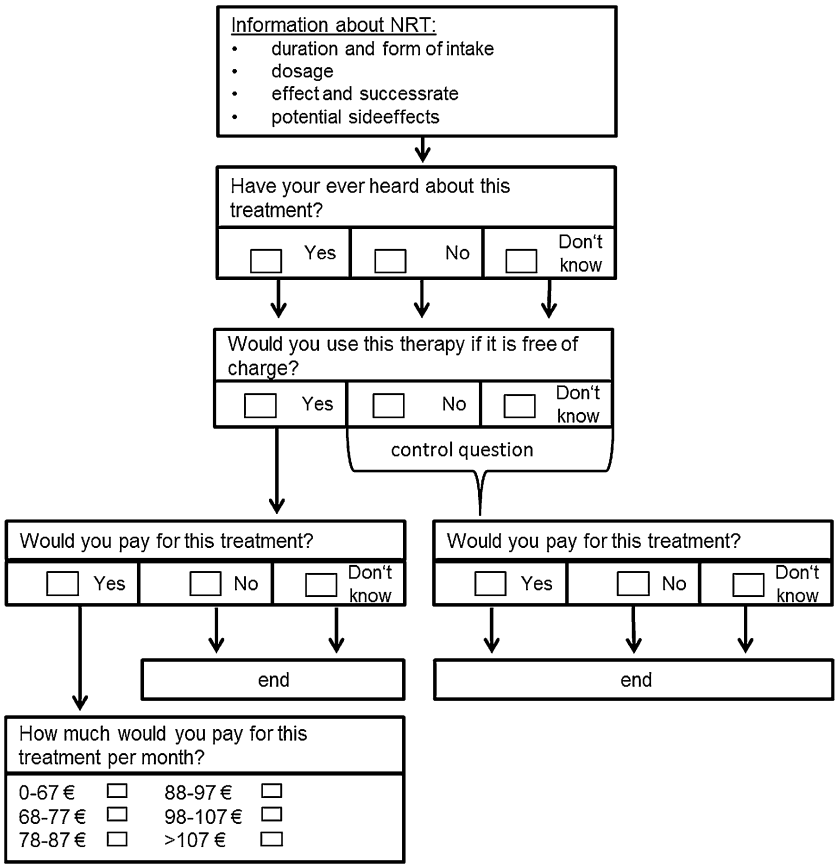

Fig. 1 Questions for assessing willingness to use and willingness to pay for nicotine replacement therapy

3 Results

3.1 Descriptive Statistics

Overall, 1735 participants clicked on the URL to the questionnaire during both periods of the survey; of these, 709 started filling it out and 505 respondents completed it. The total sample consisted of 505 individuals with a mean age of 32.63 years. It also had a well-balanced gender ratio (57.43 % male). The largest part of the sample (68.51 %) had completed their education up to high school. In terms of profession, one-third of the sample (31.88 %) is currently studying, and 55.05 % chose the option 'currently employed', which also includes self-employment.

Smoking addiction level, as assessed using the Fagerström test, was 'low' or 'low-moderate' for most of the sample (61.79 %) and 'moderate' or 'high' for the remainder (38.02 %). Most of the respondents (61.79 %) estimated the proportion of smokers in their social environment (peer group) to be between 11 and 50 %. Around 37 % of the respondents wanted to quit smoking, while the other respondents had not decided yet or did not want to quit (62.7 %).

Further details of respondents' characteristics are given in Table 1. Responses to the part of the questionnaire about smoking cessation aids show that NRT is better known than bupropion or varenicline. Most of the respondents (87.13 %) reported having heard about NRT, whereas only 12.48 and 13.07 % had heard about bupropion and varenicline, respectively. Responses to the question on experience with usage of the medications showed the same tendency: the greatest proportion of the respondents among those who have attempted to stop smoking (374 out of 505) have used NRT (19.25 %), 1 % have used bupropion and 3 % have used varenicline. The other 76.75 % did not use any pharmacological smoking cessation therapies in their last attempts to stop smoking.

Analysis of WTU for medication when it is free of charge shows that NRT is preferred over the other therapy options: more than half of the respondents expressed their willingness to use NRT and only one-third did so for bupropion and varenicline. Most of these respondents are not willing to quit smoking (77.90 % for NRT, 77.78 % for bupropion and 79.46 % for varenicline).

In contrast to WTU, half as many respondents are willing to pay for pharmacotherapy. Out of the total sample, 20.79 % are willing to pay for NRT and 12.87 % are willing to pay for bupropion and varenicline. The intervals chosen by those who responded 'yes' to WTP show that they do not want to pay the amount of the market price.

Table 1 Main characteristics of the analysis sample

$n = 505$		Percentage or mean
Sex (%)	Female	42.57
	Male	57.43
Age (years), mean (SD)		32.62 (11.62)
Health restrictions due to smoking (%)	No	63.96
	Yes	33.66
	NA	2.38
Income (%)	0–1000 €	35.45
	1001–1500 €	11.68
	1500–2000 €	14.26
	>2000 €	26.53
	NA	12.08
Primary education group (%)	Low	8.12
	Middle	22.18
	High	68.51
	NA	1.18
Employment	Employed	55.05
	Not working	11.88
	Studying	31.88
	NA	1.19
Addiction level (%)	Low	36.44
	Low–moderate	25.35
	Moderate	29.31
	High	8.71
	NA	0.59
Peer group (%)	0–10	15.45
	11–25	29.31
	26–50	32.48
	>50	19.01
	NA	3.76
Willingness to quit (%)	Yes	20.20
	Not decided	16.63
	No	62.57
	NA	0.59
Support (%) (only patients who have at least one attempt to quit smoking)	NRT	No 80.21
		Yes 19.25
		NA 0.53
	Bupropion	No 97.59
		Yes 1.07
		NA 1.34
	Varenicline	No 95.19
		Yes 3.48
		NA 1.34
Having heard about the therapy	NRT	No 12.67
		Yes 87.13
		NA 0.20
	Bupropion	No 87.13
		Yes 12.48
		NA 0.40
	Varenicline	No 85.94
		Yes 13.07
		NA 0.99

Table 1 continued

$n = 505$		Percentage or mean
Willingness to use yes (%)	NRT	52.87
	Bupropion	32.08
	Varenicline	36.63
Willingness to pay yes (%)	NRT	20.79
	Bupropion	12.87
	Varenicline	12.87
Willingness to pay intervals for NRT ($n = 105$) (%)	<67 €	58,09
	68–77 €	7.62
	78–87 €	8.57
	88–97 €	14.29
	98–107 €	7.62
	>107 €	3.81
Willingness to pay intervals for bupropion ($n = 65$) (%)	<54 €	53.85
	55–64 €	7.69
	65–74 €	12.31
	75–84 €	3.08
	85–94 €	12.31
	>94 €	9.23
Willingness to pay intervals for varenicline ($n = 80$) (%)	<76 €	71.25
	77–86 €	8.75
	87–96 €	8.75
	97–106 €	2.50
	107–116 €	2.50
	>116 €	5.00

NRT nicotine replacement therapy, *NA* not available

Most of the respondents (74.28 %) are willing to pay less than €87 for NRT, which is below the market price in Germany. Out of the 105 people who are willing to pay for NRT, 60 also state WTP for varenicline and 46 for bupropion. Although fewer smokers are willing to pay for varenicline ($n = 80$) and bupropion ($n = 65$), most of the respondents chose lower price intervals: lower than €96 and €74, respectively.

We examined the variation in WTU and WTP for the three alternative medications across different respondent characteristics. The resultant estimates are given in Tables 2, 3, 4 for each therapy. We calculated 95 % confidence intervals (CIs) to estimate the precision of the odds ratios (ORs).

3.2 Results for 'Willingness to Use' (WTU) if it is Free of Charge

Out of 11 variables, six show statistical significance at $p < 0.05$ for WTU if the medication is free of charge for NRT, five for varenicline and four for bupropion. Of these, an addiction level has the same effect on the occurrence of the answer 'yes' for all three medications: with its increase, the odds of the positive WTU ('yes') outcome rise. Results also show a few common trends across the therapies: an increasing effect of male gender and a decreasing effect of 'yes' and 'not decided' with regard to willingness to quit. Other determinants of WTU vary across the medications (Table 2). The employment variable shows statistical significance for NRT and varenicline. Compared with employed smokers, smokers who are currently studying or not working are less likely to be willing to use the smoking cessation aid.

Being familiar with medication in terms of having heard about or having used it shows an increasing effect on WTU for NRT. Opposite results are obtained for varenicline. Smokers who have used varenicline before are less likely to use it again.

3.3 Results for Positive 'Willingness to Pay' (WTP)

We conducted a logit regression to examine the effects of the respondents' characteristics on WTP in the form of binomial data. Resultant ORs are presented in Table 3. According to the resultant ORs, addiction level has a similar effect on WTP as it does on WTU: people who state stronger addiction are more likely to be willing to pay for a smoking cessation therapy. Willingness to quit shows an opposite decreasing effect on WTP.

Table 2 Summary of logistic regression analysis for willingness to use (WTU) smoking cessation therapy when it is free of charge ($n = 505$)

Predictor/reference category	Comparative category	WTU NRT				WTU bupropion				WTU varenicline			
		Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code	Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code	Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code
Intercept		0.1728	0.0404	0.7080	*	0.1913	0.0520	0.6720		0.3872	0.1040	1.4133	
Demographic and socioeconomic variables													
Age	Numeric variable	1.0215	0.9901	1.0548		1.0173	0.9877	1.0478		1.0092	0.9778	1.0416	
Gender/female	Male	1.8421	1.0926	3.1406	*	1.0501	0.6302	1.7559		1.7900	1.0699	3.0285	*
Employment/employed	Not working	0.7825	0.2358	2.6897		0.9573	0.3216	2.8213	**	0.8632	0.2902	2.6057	
	Studying	0.4071	0.1406	1.1233	.	0.4758	0.1648	1.3187		0.6596	0.2457	1.7430	
Income/1501–2000	0–1000	1.9827	0.6335	6.5485		1.5968	0.5205	5.1356		0.7415	0.2427	2.2876	
	1001–1500	1.6737	0.6079	4.7588		1.2298	0.4821	3.1479		0.9582	0.3678	2.4972	
	>2000	0.5135	0.2280	1.1285		0.7894	0.3649	1.7061		0.4228	0.1877	0.9313	*
Smoking-related variables													
Addiction level[a]/low	Low–moderate	4.5257	2.3082	9.1880	***	1.4652	0.7622	2.8125	.	2.4292	1.2800	4.6567	*
	Moderate	1.2859	0.6222	2.6592		1.8972	0.9272	3.8938		2.7282	1.3257	5.7006	**
	High	1.3914	0.6143	3.1864		2.8197	1.2773	6.3063		2.4942	1.1505	5.4766	
Health restrictions due to smoking/no	Yes	1.3572	0.7544	2.4553		1.4596	0.8446	2.5132		1.4332	0.8178	2.5119	
Peer group/11–25 %	0–10 %	1.1173	0.5026	2.5036		2.1567	1.0222	4.6071	*	1.8432	0.8613	3.9993	
	26–50 %	1.2001	0.6335	2.2845		1.3701	0.7165	2.6488		1.2719	0.6677	2.4452	
	>50 %	1.3250	0.6191	2.8643		1.4622	0.7031	3.0484		1.0682	0.5113	2.2299	
Willingness to quit/no	Not decided	0.2520	0.1163	0.5260	***	0.5777	0.2614	1.2201	**	0.5994	0.2799	1.2495	
	Yes	0.1944	0.0948	0.3845	***	0.2846	0.1211	0.6149	*	0.1721	0.0723	0.3752	***
Quit attempts	Numeric variable	1.1236	0.9979	1.2900	.	0.9988	0.9260	1.0881		1.0092	0.9356	1.0987	
Therapy-related variables													
Have heard about the therapy/No	Yes	2.5736	1.2698	5.3532	**	1.5319	0.6861	3.4718		1.9858	0.8227	5.0303	
Have used this therapy/no	Yes	2.1273	0.9027	5.4049	.	1.8668	0.0793	22.6727		0.0263	0.0013	0.1867	**
AIC	409.62					423.01				416.36			

Significance codes: 0 = ***; 0.001 = **; 0.01 = *; 0.05 = .; 0.1 = blank

NRT nicotine replacement therapy, *CI* confidence interval, *AIC* Akaike Information Criterion

[a] Based on the Frageström test

Table 3 Summary of logistic regression analysis for willingness to pay (WTP) for smoking cessation therapy ($n = 505$)

Predictor/reference category	Comparative category	WTP NRT				WTP bupropion				WTP varenicline			
		Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code	Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code	Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code
Intercept		0.0482	0.0072	0.2783	**	0.0785	0.0115	0.4758	**	0.1047	0.0182	0.5525	**
Demographic and socioeconomic variables													
Age	Numeric variable	1.0151	0.9797	1.0516		1.0098	0.9675	1.0532		1.0069	0.9670	1.0481	
Gender/female	Male	0.9953	0.5407	1.8392		0.7973	0.3781	1.6815		1.3373	0.6873	2.6476	
Employment/employed	Not working	0.1536	0.0341	0.5875	**	0.8051	0.1422	3.6815		0.8251	0.1771	3.3753	
	Studying	0.5844	0.1653	1.9572		3.1677	0.7565	12.9672		3.2527	0.8594	12.7492	.
Income/1501–2000	0–1000	0.8545	0.2203	3.4108		0.1231	0.0222	0.6577	*	0.1471	0.0301	0.6919	*
	1001–1500	1.6039	0.5285	4.8824		0.9354	0.2605	3.3056		0.8868	0.2596	2.9485	
	>2000	1.0797	0.4615	2.5700		1.8619	0.7093	5.2537		1.6659	0.6834	4.2772	
Smoking-related variables													
Addiction level[a]/low	Low–moderate	1.9837	0.9013	4.4026	.	2.4690	0.9380	6.7811	.	2.0335	0.8616	4.8773	
	Moderate	1.4862	0.6038	3.6345		1.9489	0.6635	5.8421		1.9976	0.7656	5.2238	
	High	0.9121	0.3344	2.4277		3.1081	1.0357	9.6957	*	2.0401	0.7584	5.5222	
Health restrictions due to smoking/no	Yes	1.7189	0.8949	3.3193		2.0117	0.9563	4.2622	.	2.2879	1.1609	4.5574	*
Peer group/11–25 %	0–10 %	2.6450	1.1471	6.2331	*	1.6799	0.6396	4.4109		1.1903	0.4751	2.9521	
	26–50 %	1.0927	0.5054	2.3835		0.6855	0.2684	1.7054		0.7395	0.3185	1.7055	
	>50 %	0.5451	0.1998	1.3989		0.4453	0.1269	1.3566		0.6618	0.2336	1.7522	
Willingness to quit/no	Not decided	0.1792	0.0392	0.5707	**	0.2143	0.0281	0.8825	.	0.5041	0.1363	1.4745	
	Yes	0.3074	0.0968	0.8136	*	0.4255	0.1114	1.2936		0.1679	0.0363	0.5468	**
Quit attempts	Numeric variable	1.0024	0.9071	1.0918		0.9767	0.8738	1.0658		0.9947	0.9062	1.0795	
Therapy-related variables													
Have heard about the terapy/no	Yes	3.5207	1.2403	12.2394	*	1.6082	0.6149	4.1430		1.4840	0.5427	3.9867	
Have used this therapy/no	Yes	3.5161	1.5786	8.0318	**	19.3837	0.6531	399.6316	*	0.1486	0.0072	1.0372	.
AIC	325.7					256.86				294.66			

Significance codes: 0 = ***; 0.001 = **; 0.01 = *; 0.05 = .; 0.1 = blank

NRT nicotine replacement therapy, *CI* confidence interval, *AIC* Akaike Information Criterion

[a] Based on the Fragestrom test

Table 4 Summary of interval regression analysis for willingness to pay (WTP) for smoking cessation therapy

Predictor/reference category	Comparative category	WTP NRT ($n = 105$)				WTP bupropion ($n = 65$)				WTP varenicline ($n = 80$)			
		Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code	Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code	Odds ratio estimate	Lower CI 2.5 %	Upper CI 97.5 %	Significance code
Intercept		65.6577	47.1664	91.3984		36.4853	24.7757	53.7289	***	84.8987	68.9479	104.5396	***
Demographic and socioeconomic variables													
Age	Numeric variable	1.0016	0.9955	1.0078		1.0191	1.0097	1.0285	***	1.0032	0.9989	1.0075	
Gender/female	Male	1.1201	1.0353	1.2119	*	0.9913	0.8951	1.0978		0.9808	0.9223	1.0430	
Employment/employed	Not working	1.0189	0.7827	1.3266		0.7023	0.5525	0.8926	**	0.9906	0.8203	1.1962	
	Studying	1.0359	0.7591	1.4137		0.9584	0.7634	1.2032		1.0252	0.8837	1.1894	
Income/>2000	0–1000	0.8785	0.6374	1.2107		1.0884	0.8937	1.3254		0.8899	0.7651	1.0350	
	1001–1500	0.8987	0.7802	1.0353		0.8958	0.7495	1.0707		0.9253	0.8177	1.0471	
	1501–2000	0.9948	0.8762	1.1295		0.8913	0.7642	1.0396		0.9467	0.8644	1.0370	
Smoking-related variables													
Addiction level[a]/high	Low	0.7958	0.6907	0.9168	*	0.9895	0.8107	1.2078		0.7845	0.7042	0.8740	**
	Low–moderate	0.8124	0.7263	0.9088	**	1.0210	0.8508	1.2251		0.7757	0.7080	0.8499	***
	Moderate	0.9876	0.8765	1.1129		0.9952	0.8678	1.1414		0.8144	0.7400	0.8963	**
Health restrictions due to smoking/no	Yes	0.9860	0.8901	1.0921		0.8941	0.7833	1.0205	*	0.9850	0.9160	1.0591	
Peer group/>50 %	0–10 %	1.1093	0.9546	1.2891		0.9170	0.7490	1.1227		1.0320	0.9064	1.1751	
	11–25 %	1.1132	0.9696	1.2781		0.9697	0.8209	1.1456		1.0174	0.9217	1.1229	
	26–50 %	1.0422	0.8885	1.2226		0.9986	0.8313	1.1995		1.1417	1.0185	1.2798	*
Willingness to quit/no	Not decided	0.8479	0.6856	1.0486		0.8402	0.6247	1.1302		0.9745	0.8611	1.1029	
	Yes	1.1104	0.9134	1.3499		0.9437	0.7582	1.1746		1.0477	0.9171	1.1970	
Quit attempts	Numeric variable	1.0026	0.9870	1.0184		0.9899	0.9778	1.0021		1.0052	0.9989	1.0116	
Therapy-related variables													
Have heard about the therapy/no	Yes	1.1406	0.9443	1.3777		1.2427	1.1152	1.3848	***	0.9637	0.8961	1.0365	
Have used this therapy/no	Yes	1.0151	0.9154	1.1258		0.7260	0.4964	1.0620	**	1.1518	0.9531	1.3919	.
AIC	297.5					161.8				167.6			

Significance codes: 0 = ***; 0.001 = **; 0.01 = *; 0.05 = .; 0.1 = blank

NRT nicotine replacement therapy, *CI* confidence interval

[a] Based on the Fragerström test

These results hold for the three therapies. Effects of job, income and experience of usage differ among the medications. For NRT, shifting from employed to not working status has a decreasing effect, and both having heard about NRT and having used it show an increasing effect. Additionally, peer group shows that smokers who have less than 10 % smokers in their social environment are likelier to be willing to pay for NRT as compared to those whose peer group has around 25 % smokers.

Results for bupropion also show a decreasing effect of decreasing income and an increasing effect of presence of health restrictions due to smoking. These variables have similar effects on WTP for varenicline. Additionally, smokers who are studying are likelier to be willing to pay for varenicline compared with smokers who are employed.

3.4 Results for WTP Value

Respondents who reported positive WTP also provided responses to the payment card. Values were combined to create interval data on WTP. The resultant samples differ in their sizes among the therapies. These samples are used in the regression analysis of interval WTP, with application of accelerated failure-time models. The Weibull distribution is the best-fitting distribution of the outcome variable for the three samples. Table 4 shows the obtained results and respective sample sizes. In addition to the previous regression results, several determinants of WTP are found for each therapy. For NRT, two variables show statistical significance: gender and addiction level. Men are likelier to be willing to pay more than women. A decrease in addiction level decreases the probability of being willing to pay more. Addiction shows the same effect for varenicline. A shift in peer group from '>50 %' to '26–50 %' increases the probability of a higher WTP value.

For bupropion, presence of health restrictions and a shift from employed to not working status decrease this probability. Additionally, age shows an increasing effect. The ORs show that people who have used bupropion are less likely and people who have used varenicline are more likely to be willing to pay a higher amount for these medications.

4 Discussion

In this study, we consider three smoking cessation aids which are approved by the European Medicines Agency and the US Food and Drug Administration (NRT, bupropion, andvarenicline), and investigate driving factors of WTU and WTP for each of them among young and middle-aged smokers in Germany.

Mainly we aimed to produce an analysis supporting the development of a policy which would target smoking cessation among young adults. Therefore, we focus our investigation on the existing medications which allowed us to compared WTP and current market price [26, 27]. According to our results, the amount which the majority of young and middle-aged smokers are willing to pay is lower than the market price for all therapies. The relatively high price might be related to the low prescription rates of these medications [2].

In our survey, we included both smokers who stated a willingness to quit smoking and smokers who were not willing to quit smoking. We believe that exclusion of the latter might bring a selection bias into an analysis of smokers' WTP, for instance, when comparing market price with WTP [8]. Furthermore, when a smoking cessation policy is being developed, consideration of those who are not willing to quit is desirable in order to elaborate measures directed towards enhancing motivation to quit smoking, supporting it with provision of information about available medication aids for smoking cessation.

Inclusion of the willingness-to-quit variable in our analysis shows that smokers who indicate willingness to quit are less likely to be willing to use and to pay for smoking cessation aids, contrary to our expectations. This finding is supported by a study previously conducted by Morphett et al. [28, 29]. The authors report that unassisted quitting is frequently described as the best way to quit smoking, and smokers see motivation to quit as the foundation of successful quitting, so that when a smoker is truly motivated, no medication aid is necessary.

Another explanation for this result may relate to our sample, which mostly includes people who indicate a low to moderate addiction level. Low addiction level, according to our results, decreases WTP for smoking cessation aids. The same effect is described by Nguyen at al. [30], who found in a quantitative analysis that light smokers (1–10 cigarettes per day) are less likely to believe that medications would give them a better chance of quitting, and prefer group counselling.

Overall, in our study, addiction level is found to be one of the major drivers of WTU and WTP. WTU and WTP increase with increasing addiction level. This effect has been already reported by Olsen et al. [15]; however, the authors applied the Cigarette Dependence Scale (CDS-12) to measure addiction. We used the Fagerström test and support their findings. With regard to this result, policy measures related to pharmacological smoking cessation aids (e.g. distribution and promotion information about them) should target smokers with a high addiction level, as their amount of WTP is not high enough to buy the medications. Furthermore, this group is particularly at risk of contracting a smoking-related disease. Therefore, it is necessary to support these groups of smokers first.

Generally, driving factors of WTP and WTU seem to coincide; however, they differ between therapies. Smokers who have used NRT before are more likely to use it again than are smokers who have not had this experience. For varenicline, this is not the case. This might be because of the discouraging side effects of varenicline. Etter and Schneider indicate that one-third of varenicline users report the side effects as being too strong, while only 13.5 % state the same for NRT [31].

Additionally, we investigated how the magnitude of WTP varies with individual characteristics of smokers. According to our results, most people are willing to pay for smoking cessation medication at a value less than the market cost in Germany. The average price of NRT is around €87 [32] per month, which, according to our results, is perceived as high: more than 70 % of the respondents state that they are not willing to pay that amount. Other therapy alternatives are similarly perceived as expensive by the majority of smokers. Of the respondents who are willing to pay for bupropion, only 26.15 % have a maximum WTP higher than the market price (€74 per month [32]). For varenicline, only 11.25 % are willing to pay the market price (€106 per month [32]) or more. The low magnitude of WTP for pharmacological smoking cessation therapies might be a reason for the very low prescription rate (1 %) for bupropion and varenicline [2]. According to these results, it seems that most young and middle-aged smokers in Germany are not willing to pay the market price for smoking cessation aids. Some changes in this direction might be addressed when developing a public health smoking cessation strategy, e.g. reducing the price of medications or development of co-payment options or bonus payments by health insurance companies on condition of successful quitting.

The results of the analysis show that people who are familiar with NRT therapy are likely to be willing to use it and pay for it. Promoting activities to inform smokers about available support with NRT and provision of accurate safety information can increase WTU [33, 34]. However, knowledge about NRT does not necessarily lead to a higher magnitude of WTP for NRT.

A few limitations of our study should be mentioned. First, we targeted smoking young and middle-aged adults, so the sample is not representative of the German population. Second, the results of the regression for magnitude of WTP should be interpreted with caution because of the small number of respondents who gave intervals for WTP for the therapies. Furthermore, we analyse WTP for existing medications but not hypothetical constructs; therefore, respondents' choices might be biased by awareness of the market price, though we attempted to control for this during the enrolment process. An advantage of analysing existing products is that results can be used to compare WTP with real market prices and to explain statistics like low prescription rate for the medications. Additionally, one methodological limitation is the online form of the survey, as certain population groups are less likely to fill out online questionnaires or do not have Internet access.

Further research with a representative and more heterogeneous sample is needed. Among other research questions, it remains interesting to identify the determinants of low magnitude of WTP among smokers and what policy options would increase WTP to the level of the market price. It is also necessary to explore differences in WTU and WTP between smokers who indicate willingness to quit and those who do not. A qualitative research design might be necessary to identify factors which cause these differences in behaviour. Additionally, investigation of non-monetary incentives for quitting might be needed for a better understanding of the motives and preferences of smokers.

5 Conclusion

To sum up, this study indicates four main points to be considered for development of a smoking cessation policy which pertains to pharmacological aids. First, it has to target smokers who are both willing to quit and those who are not; however, it is necessary to take into account smokers' perception of their own ability to quit and promote additional support. Second, in order to achieve a better impact, measures should be directed towards smokers with a strong addiction. Third, promotion information and improving awareness about medication aids and their efficacy might increase willingness to use them. Last, WTP for pharmaceutical smoking cessation aids is below the market price for all therapy options; therefore, development of monetary incentives for young smokers can create a better chance for successful smoking cessation.

These findings can inform development of health policies and strategies which target smoking cessation among young and middle-aged smokers.

Author contributions Ines Aumann and Niklas Hagemann developed the questionnaire, recruited the participants and prepared the data. Marina Treskova carried out the regression analyses and participated in production of the manuscript. The results and the main aspects of their interpretation were discussed by the entire research team. Ines Aumann and J. Matthias Graf von der Schulenburg obtained the positive vote from the ethics committee, and drafted and critically revised the manuscript. All the authors read and approved the final version of the manuscript.

Compliance with Ethical Standards

No funding was received for this study. Ines Aumann, Marina Treskova, Niklas Hagemann and Prof J.-Matthias Graf von der Schulenburg declare that they have no conflicts of interest. The study has

ethical approval from the Hanover Medical School (2258-2014) and was performed in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

References

1. Organization WHO. WHO Report on the Global Tobacco Epidemic 2013. Enforcing bans on tobacco advertising promotion and sponsorship. Geneva: World Health Organization; 2013.
2. TNS Opinion and Social. Attitudes of Europeans. Special Eurobarometer 385. http://ec.europa.eu/health/tobacco/docs/eurobaro_attitudes_towards_tobacco_2012_en.pdf. Accessed 27 Jul 2015.
3. World Health Organization. Global Adult Tobacco Survey (GATS). http://www.who.int/tobacco/surveillance/survey/gats/en/. Accessed 26 July 2015.
4. Centers for Disease Control and Prevention. Quitting smoking. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/index.htm#methods. Accessed 25 Jul 2015.
5. Anderson JE. Treating tobacco use and dependence. Chest. 2002;121:932.
6. Aumann I, Rozanski K, Damm K, von der Schulenburg JM. Cost-effectiveness of pharmacological smoking cessation therapies—a systematic literature review. das Gesundheitswesen 2015. doi:10.1055/s-0035-1548852.
7. Busch S, Falba T, Duchovny N, Jofre-Bonet M, O'Malley S, Sindelar J. Value to smokers of improved cessation products: evidence from a willingness-to-pay survey. Nicot Tob Res. 2004;6:631–4.
8. Heredia-Pi IB, Servan-Mori E, Reynales-Shigematsu LM, Bautista-Arredondo S. The maximum willingness to pay for smoking cessation method among adult smokers in Mexico. Value Health. 2012;15:750–8.
9. Marti J. Assessing preferences for improved smoking cessation medications: a discrete choice experiment. Eur J Health Econ. 2012;13:533–48.
10. Weimer DL, Vining AR, Thomas RK. Cost-benefit analysis involving addictive goods: contingent valuation to estimate willingness-to-pay for smoking cessation. Health Econ. 2009;18:181–202.
11. Olsen JA, Røgeberg OJ, Stavem K. What explains willingness to pay for smoking-cessation treatments—addiction level, Quit-rate effectiveness or the opening bid? Appl Health Econ Health Policy. 2012;10:407–15.
12. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet. 1994;343:139–42.
13. Fagerstrom K. Determinants of tobacco use and renaming the FTND to the Fagerstrom test for cigarette dependence. Nicot Tob Res. 2011;14:75–8.
14. Eisenberg MJ, Filion KB, Yavin D, Belisle P, Mottillo S, Joseph L, Gervais A, O'Loughlin J, Paradis G, Rinfret S, Pilote L. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. Can Med Assoc J. 2008;179:135–44.
15. Olsen JA, Smith RD. Theory versus practice: a review of 'willingness-to-paýin health and health care. Health Econ. 2001;10:39–52.
16. Bayoumi AM. The measurement of contingent valuation for health economics. PharmacoEconomics. 2004;22:691–700.
17. Klose T. The contingent valuation method in health care. Health Policy. 1999;47:97–123.
18. Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, et al. Eliciting public preferences for healthcare: a systematic review of techniques. Health Technol Assess. 2001;5:1–186.
19. Geskus RB, Groeneboom P. Asymptotically optimal estimation of smooth functionals for interval censoring, I. Statistica. Stat Neerl. 1996;50:69–88.
20. Groeneboom, P, Wellner JA. Information bounds and non-parametric maximum likelihood estimation, DMV seminar, vol 19. Basel: Birkhauser; 1992.
21. Håkansson C. A new valuation question: analysis of and insights from interval open-ended data in contingent valuation. Environ Resour Econ. 2008;39:175–88.
22. Arigoni Ortiz R, Markandya A, Hunt A. Willingness to pay for mortality risk reduction associated with air pollution in São Paulo. Rev Bras Econ. 2009;63:3–22.
23. Gelcich S, Amar F, Valdebenito A, Castilla JC, Fernandez M, Godoy C, Biggs D. Financing marine protected areas through visitor fees: insights from tourists willingness to pay in Chile. Ambio. 2013;42:975–84.
24. Arigoni Ortiz R, Hunt A, Seroa da Motta R, MacKnight V. Morbidity costs associated with ambient air pollution exposure in Sao Paulo, Brazil. Atmos Pollut Res. 2011;2:520–9.
25. Hanley N, Kristrom B. What's it worth? Exploring value uncertainty using interval questions in contingent valuation. Discussion papers. 2002; Department of Economics, University of Glasgow.
26. Bowera JA, Saadatb MA, Whitten C. Effect of liking, information and consumer characteristics on purchase intention and willingness to pay more for a fat spread with a proven health benefit. Food Qual Prefer. 2003;14:65–74.
27. Fleischman Foreit KG, Foreit JR. Willingness to pay surveys for setting prices for reproductive health products and services. 2004. http://www.popcouncil.org/. Accessed 30 Sept 2015.
28. Morphett K, Partridge B, Gartner C, Carter A, Wayne H. Why don't smokers want help to quit? A qualitative study of smokers' attitudes towards assisted vs. unassisted quitting. Int J Environ Res Public Health. 2015;12:6591–607.
29. Hammond D, McDonald PW, Fong GT, Borland R. Do smokers knowh how to wuit? Knowledge and perceived effectiveness of cessation assistance as preditors of cessation behaviour. Addiction. 2004;99:1042–8.
30. Nguyena MH, Lorraine R, Reitzel B, Kendzorc DE, Businelle MS. Perceived cessation treatment effectiveness, medication preferences and barriers to quitting among light and moderate/heavy homeless smokers. Drug Alcohol Depend. 2015;153:341–5.
31. Etter J, Schneider NG. An internet survey of use, opinions and preferences for smoking cessation medications: nicotine, varenicline, and bupropion. Nicot Tob Res. 2013;15:59–68.
32. Compu Group. Lauer Fischer: Lauer-Taxe—information for pharmaceuticals. http://www2.lauer-fischer.de/produkte/lauer-taxe/lauer-taxe/. Accessed 27 Jul 2015.
33. Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker's willingness to use nicotine replacement therapy as part of a quit attempt. Addict Behav. 2011;36:713–6.
34. Bansal MA, Cummings KM, Hyland A, Giovino GA. Stop-smoking medications: Who uses them, who misuses them, and who is misinformed about them? Nicot Tob Res. 2004;6:S303–10.

Supplemental Digital Content

Appendix A: Translated questionnaire

Page / No	Questions
1/0	Dear Participants, The following questionnaire is addressed to you as a smoker. To quit smoking is often a difficult task and can be supported by different types of medicine. We would like to present you with the following different medicines that can help you stop smoking. The questionnaire will only take a few minutes to complete, please make sure to read the questions carefully. Your answers will be evaluated anonymously. Participants must be 18 or older to participate in the study. Non-smokers or smokers undergoing a smoking cessation therapy cannot participate in the study. But we thank you for your interest. Thank You in advance for your participation!
2/1	Before we start, we need some information about your smoking status. How old were you when you started smoking? If the exact age is unknown please write in an approximation _____ Years old
2/2	Have you ever tried to quit smoking and if so how many times. • No ☐ • Yes ☐ _____ times
2/3	Have you tried to quit smoking through the following forms: No / yes / No response • Behavior Therapeutic Measures (ex: Group Therapy or Individual Therapy) ☐ ☐ ☐ • Medicament: Nicotine ☐ ☐ ☐ • Medicament: Bupropion ☐ ☐ ☐ • Medicament: Varenicline ☐ ☐ ☐ • Other types of medicine ☐ ☐ ☐ • Other types of Therapy (ex: Acupuncture, Hypnoses, etc) ☐ ☐ ☐
2/4	Do you have any health problems due to smoking? (Illnesses, shortness of breath, etc.) • Yes ☐ • No ☐ • No Response ☐
2/5	How much percentage of your social circle (Friends, Family, co-workers) are smokers? • 0-10% ☐ • 11-25% ☐ • 26-50% ☐ • >50% ☐ • No Response ☐
2/6	Do have any interest in quitting smoking? Yes / maybe yes / undecided / maybe No / No • I would like to quit smoking ☐ ☐ ☐ ☐ ☐

3/7	Now we will show you three different types of medicine used to quit smoking. Please read through the following therapy information carefully and then answer the following questions.
3/7	Therapy 1 Therapy Information: Medicine: Nicotine Administration type/ duration/ doses: Patch; 3 months; 1 patch per day Effectiveness: 15.4 % of the patients have quit smoking after a year (For Comparison: about 5% have successful quit smoking without the help of medications.) Possible Side Effects: Basically no other Nicotine side effects than smoking, but skin lesions can appear at the site of the patch.
3/7	Have you ever heard of Nicotine Therapy with Nicotine Patches? • Yes ☐ • No ☐ • No Response ☐
3/8	Would you pay for a Nicotine therapy with Nicotine patches? • Yes ☐ and if so how much? ○ <67€ ☐ ○ 68-77€ ☐ ○ 78-87€ ☐ ○ 88-97€ ☐ ○ 98-107€ ☐ ○ >107 ☐ • No ☐ • No Response ☐
3/9	Would you use the Nicotine Therapy with Nicotine patches if it was free? • Yes ☐ • No ☐ • No Response ☐
4/10	Therapy 2 Therapy Information: Medicine: Bupropion, sold in Germany under the brand name Zyban Administration type/ duration/ doses: Tablet; 8 weeks; In the first week 1 tablet per day, then 2 tablets per day. Effectiveness: 15.9 % of the patients have quit smoking after a year (For Comparison: about 5% have successful quit smoking without the help of medications.) Possible Side Effects: occurring in more than 1 in 10 people: Insomnia, Headache, dry mouth, nausea, vomiting.
4/10	Have you ever heard of the Medical Therapy with Bupropion? • Yes ☐ • No ☐ • No Response ☐
4/11	Would you pay for the Medical Therapy with Bupropion? • Yes ☐ and if so how much? ○ <54€ ☐ ○ 55-64€ ☐ ○ 65-74€ ☐ ○ 75-84€ ☐ ○ 85-94€ ☐ ○ >94 ☐ • No ☐ • No Response ☐

4/12	Would you use the Medical Therapy with Bupropion if it was free? • Yes ☐ • No ☐ • No Response ☐
5/13	Therapy 3 Therapy Information: Medicine: Varenicline, sold in Germany under the brand name Champix Administration type/ duration/ doses: Tablet; 12 weeks; In the first week 1 tablet per day, then 2 tablets per day. Effectiveness: 22.9 % of the patients have quit smoking after a year (For Comparison: about 5% have successful quit smoking without the help of medications.) Possible Side Effects: occurring in more than 1 in 10 people: Insomnia, Headache, abnormal dreams, nausea.
5/13	Have you ever heard of the Medical Therapy with Varenicline? • Yes ☐ • No ☐ • No Response ☐
5/14	Would you pay for the Medical Therapy with Vareniclin? • Yes ☐ and if so how much? ○ <76€ ☐ ○ 77-86€ ☐ ○ 87-96€ ☐ ○ 97-106€ ☐ ○ 107-116€ ☐ ○ >116 ☐ • No ☐ • No Response ☐
5/15	Would you use the Medical Therapy with Varenicline if it was free? • Yes ☐ • No ☐ • No Response ☐
6/16	After waking up in the morning how long do you wait before lighting your fist cigarette? • After 5 minutes ☐ • After 6-30 minutes ☐ • After 31-60 minutes ☐ • After more than 60 minutes ☐
6/17	Do you find it hard to not smoke in smoking-free areas? • Yes ☐ • No ☐
6/18	Which cigarette would you not want to give up? • The first in the morning ☐ • Other ☐
6/19	Generally, how many cigarettes do you smoke per day? • 0-10 ☐ • 11-20 ☐ • 21-30 ☐ • 31 or more ☐
6/20	Do you generally smoke more in the morning than during the rest of the day? • Yes ☐ • No ☐
6/21	Does it happen that you smoke more when you are sick and need to stay in bed all day? • Yes ☐ • No ☐

7/22	What is your gender?	
	• Female	☐
	• Male	☐
7/23	What is your age?	
	• I am _____ Years old	
7/24	Insurance status?	
	• insured under a statutory insurance	☐
	• private insurance	☐
7/25	What is your highest academic degree?	
	• Main / primary school completion	☐
	• General certification of secondary school	☐
	• Advanced technical college entrance qualification	☐
	• General or technical University entrance qualifications	☐
	• No school qualifications	☐
	• Other _____	☐
	• No response	☐
7/26	What is your highest professional degree?	
	• Completed Professional-company training (apprenticeship)	☐
	• Completed Professional-school education (Technical school, commercial school)	☐
	• Training at a specialized school (Technical school)	☐
	• Completed a degree at a polytechnic college	☐
	• University degree	☐
	• Still doing my professional training (Professional trainee, Student , intern)	☐
	• No professional Training	☐
	• Other _____	☐
	• No response	☐
7/27	What is your current job status?	
	• Employed or Self-employed	☐
	• In company training/education or occupational retraining	☐
	• Federal Voluntary Service/ Voluntary Social Year	☐
	• Pension	☐
	• Stay at home Mom/Dad	☐
	• College Student	☐
	• High School Student	☐
	• Unemployed due to Medical Reasons	☐
	• Unemployed or in search of a job	☐
	• Other _____	☐
	• No response	☐
7/28	What is your monthly net income?	
	• 0-500€	☐
	• 1001-1500€	☐
	• 1501-2000€	☐
	• 2001-2500€	☐
	• >2500€	☐
	• No response	☐

Appendix B: Regression Equations

To fulfill the aim of determining the driving factors WTP and WTP different multiple regression models were employed.

For the dichotomous outcomes of WTP and WTU, we applied logit regressions. The model in general form was specified as follows:

Let variable Y_i denote WTP (WTU) which takes on two values, 0 and 1, representing whether a responder *i* is willing to pay for (willing to use) the smoking cessation aid. Let $X=(X_1,X_2,X_3...X_j)$ be a set of explanatory variables. The binary logistic regression for WTP (WTU) estimates the probability that WTP (WTU) is present given the values that the predictors take (x_{ij}).

$$Y_i = \begin{Bmatrix} 0\ if\ no \\ 1\ if\ yes \end{Bmatrix} \text{ and } Y_i \sim Bin(n_i, \pi_i)\ ,\ \pi_i = \Pr(Y_i = 1 | X_{ij} = x_{ij})$$

The logit models of the following general form were estimated for WTP and WTU for each smoking cessation aid:

$$\text{logit}(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_j X_{ij}$$

The set of the explanatory variables for WTU and WTP was defined as *X* = (age, gender, income, employment, addiction level, health restrictions due to smoking, peer group, willingness to quit, attempts to quit smoking, having heard about the therapy, have used this therapy). The regressions were estimated using *glm* function of the statistical software R.

For the WTP interval bids accelerated failure–time models were applied. The accelerated failure time model in general form was specified as a linear model of relationship between the logarithm of the WTP interval bids and the predictors:

$$\log(WTP_i) = \beta_j X_{ij} + \varepsilon_i$$

Where ε_i is a random error which determines the probabilistic behaviour of WTP and is assumed to follow the Weibull distribution.

The set of the predictors for the interval regression was analogously defined as *X* = (age, gender, income, employment, addiction level, health restrictions due to smoking, peer group, willingness to quit, attempts to quit smoking, having heard about the therapy, have used this therapy).

The accelerated failure time models were estimated for each therapy using *survreg* function of the "survival" package in R.

The Akaike information criterion (AIC) given in the summary tables (Table2, Table3, Table4) presented the goodness-of-fit values.

Article 3

Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe

Kuhlmann A, Schmidt T, Treskova M, López-Bastida J, Linertová R, Oliva-Moreno J, Serrano-Aguilar P, Posada-de-la-Paz M, Kanavos P, Taruscio D, Schieppati A, Iskrov G, Péntek M, Delgado C, Graf von der Schulenburg J-M, Persson U, Chevreul K, Fattore G

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ORIGINAL PAPER

Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe

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Abstract
Objective The aim of this study was to determine the economic burden from a societal perspective and the health-related quality of life (HRQOL) of patients with juvenile idiopathic arthritis (JIA) in Europe.
Methods We conducted a cross-sectional study of patients with JIA from Germany, Italy, Spain, France, the United Kingdom, Bulgaria, and Sweden. Data on demographic characteristics, healthcare resource utilization, informal care, labor productivity losses, and HRQOL were collected from the questionnaires completed by patients or their caregivers. HRQOL was measured with the EuroQol 5-domain (EQ-5D-5L) questionnaire.
Results A total of 162 patients (67 Germany, 34 Sweden, 33 Italy, 23 United Kingdom, 4 France, and 1 Bulgaria) completed the questionnaire. Excluding Bulgarian results, due to small sample size, country-specific annual health care costs ranged from €18,913 to €36,396 (reference year: 2012). Estimated direct healthcare costs ranged from €11,068 to €22,138; direct non-healthcare costs ranged from €7837 to €14,155 and labor productivity losses

Members of the BURQOL-RD Research Network listed in Supplementary Annex 1.

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ranged from €0 to €8715. Costs are also shown to differ between children and adults. The mean EQ-5D index score for JIA patients was estimated at between 0.44 and 0.88, and the mean EQ-5D visual analogue scale score was estimated at between 62 and 79.

Conclusions JIA patients incur considerable societal costs and experience substantial deterioration in HRQOL in some countries. Compared with previous studies, our results show a remarkable increase in annual healthcare costs for JIA patients. Reasons for the increase are the inclusion of non-professional caregiver costs, a wider use of biologics, and longer hospital stays.

Keywords Rare diseases · Juvenile idiopathic arthritis · Costs · Costs of illness · Quality of life

JEL Classification I1

Introduction

Juvenile idiopathic arthritis (JIA) is a general term for a group of conditions characterized by chronic arthritis with no defined cause. The disease commonly occurs in children before the age of 16 and lasts for a minimum of 6 weeks. According to the results of the International League of Associations for Rheumatology (ILAR) Meeting in 2001, JIA combines the following seven subtypes: systemic arthritis, oligoarthritis, rheumatoid-factor-negative polyarthritis, rheumatoid-factor-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. These subtypes represent heterogeneous and autonomous diseases, apart from the undifferentiated arthritis, which defines diseases that cannot be classified or are related to more than one of the above subtypes [1]. The prevalence in Europe ranges from 4.2 to 20.5 per 100,000, depending on the specific subtype [2]. Country-specific values are not available.

The progression of JIA varies across the subtypes in terms of the number and type of inflamed joints, type of complication (fever or rash), time of occurrence, and the duration. Consequently, children with JIA are under threat of suffering from long-term complaints like joint destruction. Treatment of JIA is subject to the subtype. In general, it combines drug treatment, physiotherapy, occupational therapy, and, if required, psychological therapy [1]. The drug therapy covers a broad spectrum of medicines, e.g., non-steroidal anti-inflammatory agents, intra-articular corticosteroid injections, disease-modifying anti-rheumatic drugs, anti-interleukin therapy, and biologics. The choice of medication depends on the subtype of JIA [3].

The aim of this study was to estimate JIA-related social/economic costs in Europe. We provide analysis of the related costs, including direct healthcare costs, direct non-healthcare costs (formal and informal care) and loss of labor productivity. We quantify health-related quality of life (HRQOL) for patients with JIA and JIA-related non-professional caregivers. We provide our analysis on samples obtained during 2012 from eight EU countries.

Methodology

Research design and subjects This was a cross-sectional study of people diagnosed with JIA who received outpatient care and were living in the community. All patients and caregivers were informed about the study objectives and data confidentiality and were asked to state their understanding of the study conditions and agreement to participate. Cases were recruited from the specific JIA associations and registries. The survey was completely anonymous, as the patients were contacted by their patient organization and their responses were sent directly to the researchers without any identification data (name, identification, address, e-mail).

Information and variables of interest The fieldwork was carried out between September 2011 and April 2013. Questionnaires were administered by e-mail and postal survey through patient organizations. The information sources used in the study were the self-completed questionnaire filled out by patients and their caregivers. Demographic and clinical data were collected from patients diagnosed previously with JIA and their caregivers.

Most studies of cost-of-illness and HRQOL use information gathered at a specific point in time. The questionnaire we used was detailed enough to reduce either exaggeration or underestimation. To estimate resource utilization, the questionnaire solicited information covering the 6-month period prior to the study (12 months for hospitalizations). Data for the preceding 6 months were extrapolated to the entire year. We considered 6 months to be an appropriate recall period. Patients and caregivers were asked about reductions in working time (temporary and permanent sick leave or early retirement), and these data were used to estimate losses of labor productivity. Also, when care was provided by non-professional caregivers, they were asked about the informal care time. Information about HRQOL was collected from JIA patients through the generic EuroQol 5-domain (EQ-5D) questionnaire [4].

Costing methodology We used the prevalence approach to estimate costs from a societal perspective. Disease prevalence takes into account all existing cases during a given year and all health care resources used for prevention, treatment and rehabilitation, plus other resources used (formal and informal care) or loss of labor productivity

within that year as a consequence of the illness considered. Prevalence-based cost-of-illness analysis has the advantage of incorporating measurements of total annual healthcare expenditure, which is particularly relevant for chronic conditions such as JIA that require long-term treatment. In this context, a bottom-up costing approach was used to estimate total and average annual costs [5].

Data on resource utilization were collected for each patient. The resources used were multiplied by unit costs to estimate the annual cost per patient, with 2012 as the reference year.

Direct healthcare costs Direct costs were derived from healthcare utilization. The value of resources used by patients was calculated in terms of the relevant unit costs and the average cost per patient in the sample. Information about the number of hospital admissions was obtained from the questionnaires.

Data for the volume of outpatient care (rehabilitation, medical tests and examinations, visits to health professionals, and home medical care) and the number of emergency visits were obtained from the questionnaires. Unit costs that were obtained from different sources and healthcare cost databases (see Supplementary Annex 2) were then multiplied by the units of each resource used. Information regarding the medications used by patients with JIA was obtained from the questionnaires. The cost of drugs used by patients was calculated by determining the daily cost for each of the products used (based on the cost of each pack dispensed and the dose used) and then multiplying by duration of use. When no information concerning the number of units per pack was available, we assumed the largest pack-size was dispensed. The costs of prescription drugs used were obtained from the list of approved drugs in the different countries (see Supplementary Annex 2).

Information concerning the use of orthopedic devices and healthcare-related transportation was obtained from the questionnaires. The costs of orthopedic devices were obtained from different distribution firms.

Direct non-health care costs Informal care is defined as the performance of tasks by non-professionals that help maintain or enhance patient independence. Informal services are therefore defined as the group of tasks or care provided by non-professional caregivers, who are often relatives but may also be friends or neighbors. Information about informal care was obtained from the questionnaires, specifically from the items concerning the time spent helping the patient with his or her basic activities of daily living and the time spent helping with necessary instrumental activities of daily living (recall method). As a conservative criterion, and for preventing conjoint production, we have censored the time of care to a maximum of 16 h per day (112 h per week) when the time of care reported exceeded this figure.

The approach used to value the care hours was the proxy good method, which values time as an output. This method values the care provided by the informal caregiver considering that if he/she did not provide these services, their presence would have to be substituted by another person who could provide them [6]. Therefore, we took into consideration the question of how much it would cost to take on said substitution or replacement by hiring a professional caregiver [7].

Information on formal paid care provided by professional caregivers and other social services was obtained from the questionnaires and comes under the category of social services. Data on unit costs were provided by different sources (see Supplementary Annex 2).

Loss of labor productivity Data on loss of labor productivity were obtained from physical units converted into monetary units with a human capital-based approach [8]. According to human capital theory, the average earnings (gross wages) of a worker can be considered a good proxy for labor productivity losses. Therefore, our calculations were based on average gross wage figures in the Wage Structure Surveys by the National Statistics Institutes of the participating countries. Annual losses of labor productivity were estimated for the year 2012.

Patient and caregiver outcomes Patient and caregiver outcomes were obtained by means of self-administered questionnaires such as the EQ-5D, the Barthel index, and Zarit burden interview. The EQ-5D is a simple generic instrument developed by a multidisciplinary group of researchers [9]. This questionnaire has been validated in many countries in Europe, and is commonly used in economic evaluation and health technology assessment. There are five dimensions in the EQ-5D covering the areas of mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression. A total of 245 possible health states can be defined in this way. Evaluations of these health states have been reported for the general population [9]. The values or utilities are indicated on a scale on which death has a value of 0 and perfect health a value of 1, with negative values being possible.

The Barthel index is a widely used tool for the assessment of disability and measures the ability of a person to perform ten basic activities of daily living, providing a quantitative estimate of the subject's degree of dependence [10, 11]. It is easy to apply, has a high degree of reliability and validity, is capable of detecting changes, and is easy to interpret. The Barthel index is recommended as the instrument of choice for measuring physical disability, both in clinical practice and public health research. A score of 91–99 shows mild dependence, 61–90 moderate

Table 1 Characteristics of the study participants

	Bulgaria	France	Germany	Italy	Sweden	UK
Patients						
No of responses	1	4	67	33	34	23
Mean age (SD)	5.0 (NA)	6.5 (3.9)	13.1 (7.2)	10.5 (4.6)	14.5 (7.9)	21.4 (16.8)
Mean age at diagnosis, years (SD)	5.0 (NA)	4.3 (4.7)	8.8 (6.3)	4.2 (4.0)	7.7 (5.7)	5.2 (4.4)
Female (%)	0 (0)	1 (25)	47 (70.1)	26 (78.8)	26 (76.5)	18 (78.3)
Informal caregivers						
No of responses	1	2	16	9	12	8
Mean age (SD)	33.0 (NA)	47.0 (4.2)	34.5 (13.1)	41.7 (11.3)	37.6 (10.0)	43.1 (9.7)
Female (%)	1 (100)	1 (50.0)	13 (81.3)	6 (66.7)	11 (91.7)	7 (87.5)
Relationship to patient						
Parent to the patient	0	0	14	0	1	1
Other relative to the patient	1	2	2	8	11	6
Partner or other	0	0	0	1	0	0
Informal caregivers, hours per a week (SD)	0.0 (NA)	15.8 (22.3)	52.0 (41.1)	29.3 (26.8)	22.9 (32.8)	25.3 (23.8)
Health outcomes						
Utilities adult patients (SD)	NA	NA	0.729 (0.139)	NA	0.642 (0.128)	0.262 (0.239)
Utilities caregivers (SD)	0.649 (NA)	0.377 (NA)	0.745 (0.259)	0.799 (0.144)	0.594 (0.105)	0.663 (0.367)
VAS adult patients (SD)	NA	NA	60.2 (19.2)	NA	56.1 (18.6)	49.0 (12.4)
VAS caregivers (SD)	50.0 (NA)	65.0 (NA)	71.6 (20.2)	78.3 (17.1)	69.8 (15.6)	67.1 (26.1)
Barthel index (patients) (SD)[a]	NA	97.5 (3.5)	93.4 (13.1)	97.2 (7.9)	89.3 (14.3)	80.9 (18.1)
Zarit scale (caregivers) (SD)	NA	50.0 (8.5)	24.6 (11.9)	16.4 (6.7)	30.9 (15.4)	22.9 (6.6)

[a] Barthel scores for Sweden and UK were re-escalated from 20-point scale to 100-point scale

dependence, 21–60 severe dependence, and <20 complete dependence [11].

Caregivers also completed the Zarit Burden Interview (22-item version), which measures the subjective burden among caregivers. Each item is a statement which the caregiver is asked to respond to using a 5-point scale, with options ranging from 0 (never) to 4 (nearly always) [12]. The total score ranges from 0 to 88, with scores under 21 corresponding to little or no burden and scores over 61 to severe burden.

Results

One hundred and sixty-two questionnaires from six countries were collected within the study. The largest number of questionnaires (67) was obtained from Germany. Italy and Sweden contributed equally to the total sample, providing 33 and 34 filled out questionnaires, respectively. The rest were obtained from the UK (23), France (four), and Bulgaria (one). The latter was excluded from further analysis due to the low response rate.

The resultant total sample consisted of 161 patients with JIA. The major part of the sample was children and adolescents (78 %) with a mean age of 14 years. Comparison between countries of mean ages and numbers of adults showed that the samples from France and Italy consisted only of children and patients in the UK sample were, on average, older than those from the other countries.

In contrast to the age of the patients, gender distribution in the samples did not significantly vary across the countries, with females accounting for 70.1 to 78.8 % in the total sample. The sample from France was an exception and contained only one female participant (25 %).

The overall sample also included the responses of 47 informal caregivers. Response rate varied across the countries, with the largest number of responses obtained from Germany (16), followed by Sweden (12), Italy (nine), the UK (eight), and France (two). The age of the caregivers ranged from 34.5 (Germany) to 47.0 (France), with a mean of 38.8 years. The share of female carers varied from 50.0 % in France to 91.7 % in Sweden. In total, 16 caregivers were parents and 29 were relatives. The amount of care provided ranged from 16 h a week in France to 52 in Germany, with the average being 34 h per week. Table 1 summarizes the samples obtained from each country.

We quantified HRQOL for patients with JIA and for non-professional caregivers using different approaches. Table 1 summarizes the resultant estimates.

Estimates of the patients' HRQOL calculated using the EQ-5D instrument (TTO tariff) differed among Germany, Sweden, and the UK. Although patients' HRQOL showed relatively high values in the German (0.729) and the

Table 2 Average annual costs per patient, all patients (2012, €)

Costs € 2012	Bulgaria		France		Germany		Italy		Sweden		UK	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drugs	0	NA	6585	7521	6227	9044	15,522	29,368	11,524	12,410	6667	9206
Medical tests	49	NA	397	239	386	343	152	264	986	1503	2493	2662
Medical visits	427	NA	3073	4170	3919	3771	1681	1609	7770	8582	4169	3206
Hospitalizations	2262	NA	974	1948	5331	6278	3454	6000	1310	2387	1047	2962
Health material	0	NA	40	79	227	1022	0	0	47	830	114	162
Healthcare transport	21	NA	0	0	70	394	0	0	76	262	19	91
Direct healthcare costs	2759	NA	11,068	3663	16,161	12,705	20,808	34,092	22,138	17,245	14,508	14,877
Professional carer	0	NA	0	0	20	165	0	0	0	0	597	2546
Non-healthcare transport	91	NA	219	320	249	278	187	319	630	719	75	143
Social services	0	NA	0	0	1210	6599	26	146	3772	8928	50	241
Direct non-healthcare formal costs	91	NA	219	320	1479	6593	212	337	4402	9442	722	2532
Main informal carer	0	NA	4106	8213	8420	20,144	4043	9533	7081	19,228	5661	11,722
Other informal carers	0	NA	3520	7039	1483	6272	3583	9355	2673	7360	1940	9027
Direct non-healthcare informal costs	0	NA	7626	15,252	9903	24,271	7625	18,436	9753	25,999	7601	18,703
Direct non-healthcare costs	91	NA	7845	15,157	11,382	24,989	7837	18,437	14,155	30,405	8323	18,665
Direct costs	2850	NA	18,913	12,277	27,543	28,022	28,645	42,218	36,293	40,737	22,831	24,728
Sick leave	0	NA	0	0	91	465	0	0	103	599	190	513
Early retirement	0	NA	0	0	0	0	0	0	0	0	8525	14,673
Labor productivity losses patients	0	NA	0	0	91	465	0	0	103	599	8715	14,566
Total costs	2850	NA	18,913	12,277	27,634	28,008	28,645	42,218	36,396	40,742	31,546	28,568

Swedish (0.642) samples, variating inconsiderably from each other, the UK patients' HRQOL took a significantly lower value of 0.262.

Similarly to the patients with JIA, the caregivers were seen to have quality of life below 1.0 value, however, comparison between the estimates of the patients' HRQOL and the caregivers' HRQOL brought no clear inference about the existence of correlation between them. Considering the samples separately, the caregivers' HRQOL estimate obtained in the UK (0.663) was considerably higher than the patients' HRQOL (0.262); in Germany, it minimally differed from the patients' one, being 0.016 units higher (0.745); in Sweden, on opposite it was slightly lower, and took a value of 0.594. Overall, among all countries in the study, the estimates of the caregivers' HRQOL ranged from 0.594 to 0.799, with exception of the French sample, which showed the lowest value (0.377).

HRQOL estimates obtained over the total sample using EQ-5D showed a mean value of 0.56 for the patients and 0.7 for the caregivers.

Estimates of HRQOL calculated with the VAS scale showed a different pattern. According to this scale, the patients' quality of life was seen to considerably lower than that of the caregivers across all samples.

Additionally, HRQOL was analyzed applying the Barthel index and the Zarit scale. The Barthel index yielded scores 80.9 (UK) to 97.5 (France) with an average for the total sample of 91.5. The ranges in the Zarit scale values varied from country to country, from 16.4 in Italy to 50.0 in France, with a mean of 25.1 for the total sample.

Annual costs Resultant annual total costs varied from €18,913 in France to €36,396 in Sweden, with a mean for the total sample of €30,034 (±SD 33,945) per patient. The largest cost fraction was direct healthcare costs, taking up over 50 % of the total cost across all countries except the UK. Although the direct healthcare costs fraction for the UK was 46 %, they had the highest percentage of lost productivity (27.6 %), due to having the largest number of adults in the sample. The percentage of direct non-healthcare costs varied from country to country, with the lowest in the UK sample (26 %) and the highest in the French sample (41.48 %). Table 2 summarizes total annual costs and costs in each cost fraction for each country.

Although the structure of the direct healthcare differed across the countries, expenditures for medication constituted the largest share for all samples. The next largest fraction differed from country to country, but was either medical visits or hospitalization. The UK sample had the largest share of aggregated expenses for healthcare

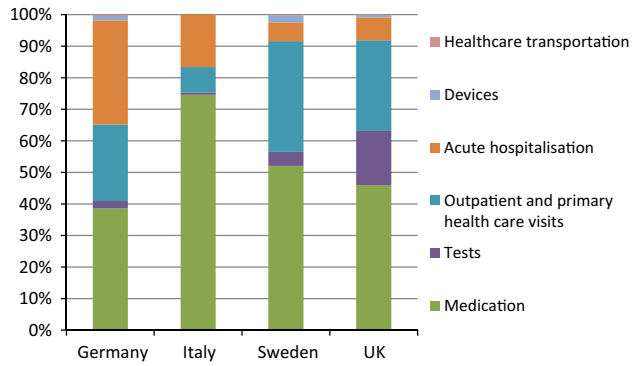

Fig. 1 Direct healthcare costs

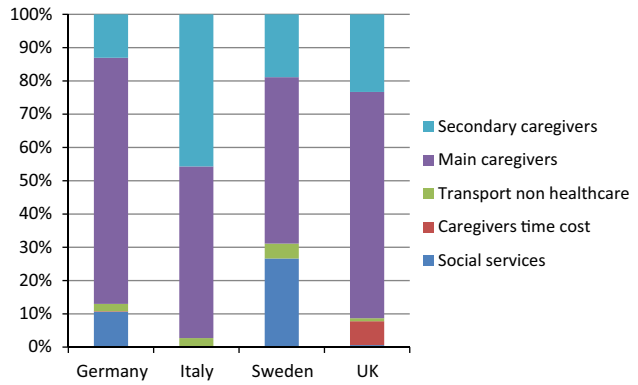

Fig. 2 Direct non-healthcare costs

transportation, health material, and medical tests (18 %). The fractions of direct healthcare costs are illustrated in Fig. 1.

The main part of direct non-healthcare costs in all countries was for informal caregivers plus professional carers, ranging from 68.90 % in Sweden to 98.49 % in the UK. Another direct non-healthcare cost fraction, social services, showed no similarities across the countries, ranging from 0 % in the French sample to 26.65 % in Sweden.

Among all fractions of direct non-healthcare costs, transportation costs were the smallest, varying from 0.9 % (UK) to 4.45 % (Sweden). The direct non-healthcare costs are presented in Fig. 2.

When looking specifically at the costs incurred by adults (36 patients), the data were included in the analysis based on the sample sizes of the UK, France, Germany, Sweden, and Italy. Mean annual costs ranged from €15,201 per patient in Sweden to €40,940 in the UK (Table 3). Direct healthcare costs ranged from €10,504 per patient in Sweden to €20,985 in Germany and direct non-healthcare costs ranged from €1933 per patient in Germany to €5116 in the UK (Table 3). Loss of labor productivity costs ranged from €349 per patient in Sweden to €20,045 in the UK (Table 3).

For pediatric patients, 125 were included in the analysis. Mean annual costs ranged from €18,913 per patient in France to €45,227 in Sweden (Table 4). Direct healthcare costs ranged from €11,068 per patient in France to €26,985 in Sweden and direct non-healthcare costs ranged from €7837 per patient in Italy to €18,242 in Sweden (Table 4).

Discussion

In this study, we analyzed JIA-related healthcare costs and quality of life based on the samples obtained from six European countries. We estimated direct healthcare and non-healthcare costs and labor productivity losses and quantified HRQOL for patients with JIA and their non-professional caregivers. We compared differences between the countries and analyzed the collected sample as a whole.

The study populations included show some heteroscedasticity in terms of the sample size and age. Given that the number of participants in Italy, Sweden, and the UK was similar, the sample from France provided four questionnaires and the sample obtained for Germany had the largest size, estimates of JIA-related costs and HRQOL obtained for the total sample are driven by the German study population.

Furthermore, the age structure of the UK sample significantly differed from other countries. The main difference lies in the number of adults who participated in the survey. In the UK sample, the number of adults was almost twice that of any other country, whereas the French and Italian samples contained no adult population. In contrast to the age structure, the gender ratio did not significantly vary from country to country, except for France, where the sample only consisted of four patients, with one female.

While there was a moderate difference in the mean age between Italy, Germany, and Sweden, the gap between the UK and the other countries ranged from 6.9 to 10.9 years. This can be explained by the differences in the number of adult participants, with adults making up 43.48 % of the UK sample but comparatively less of the samples from Germany and Sweden, with 23.88 and 29.41 %, respectively. In comparison with these countries, the samples obtained from Italy and France contain a younger population with a mean age of 10.5 and 6.6 years, respectively. The difference in the estimates of the mean age ranged from 4 to 8 years, determined by the absence of adult patients in the French and Italian samples.

Weekly amount of care and relationship between informal caregivers and the patients also varied from country to country. The samples from Italy, Sweden, and the UK reported the average amount of care to be from 22.9 to 29.3 h per week. These samples also showed that patients receive mostly non-parental care. The share of the informal caregivers with other relationships to patients ranges from 75 to

Table 3 Average annual costs per adult patient, adult patients (2012, €)

Costs € 2012	UK ($N = 10$)	France ($N = 0$)	Germany ($N = 16$)	Sweden ($N = 10$)	Italy ($N = 0$)
Drugs	6313	–	11,542	8	–
Medical tests	3226	–	278	1583	–
Medical visits	4102	–	5504	7033	–
Hospitalizations	1887	–	3563	1343	–
Health material	207	–	85	414	–
Healthcare transport	43	–	13	124	–
Direct healthcare costs	15,779	–	20,985	10,504	–
Professional carer	1372	–	0	0	–
Non-healthcare transport	110	–	333	474	–
Social services	0	–	8	2737	–
Main informal carer	3633	–	1592	1137	–
Other informal carers	0	–	0	0	–
Direct non-healthcare costs	5116	–	1933	4348	–
Direct costs	20,895	–	22,917	14,852	–
Productivity loss patients	437	–	383	349	–
Early retirement patients	19,609	–	0	0	–
Indirect costs	20,045	–	383	349	–
Total costs	40,940	–	23,300	15,201	–

Table 4 Average annual costs per pediatric patient, pediatric patients (2012, €)

Costs € 2012	UK ($N = 13$)	France ($N = 4$)	Germany ($N = 51$)	Sweden ($N = 24$)	Italy ($N = 33$)
Drugs	6939	6585	4560	16,322	15,522
Medical tests	1929	397	420	737	152
Medical visits	4220	3073	3422	8077	1681
Hospitalizations	401	974	5886	1296	3454
Health material	42	40	271	496	0
Healthcare transport	0	0	88	57	0
Direct healthcare costs	13,531	11,068	14,648	26,985	20,808
Professional carer	0	0	27	0	0
Non-healthcare transport	48	219	223	694	187
Social services	89	0	1587	4204	26
Main informal carer	7220	4106	10,562	9557	4042
Other informal carers	3432	3520	1948	3786	3583
Direct non-healthcare costs	10,789	7845	14,346	18,242	7837
Direct costs	24,320	18,913	28,994	45,227	28,645
Productivity loss patients	0	0	0	0	0
Early retirement patients	0	0	0	0	0
Indirect costs	0	0	0	0	0
Total costs	24,320	18,913	28,994	45,227	28,645

100 %. Germany stands apart from these countries, reporting significantly larger estimates for both the share of parental care (87.5 %) and the weekly amount of care (52 h), which results in considerably higher time expenditure.

We found that JIA had a significant impact on the HRQOL of patients and their caregivers regardless of the country. In adults, direct healthcare costs, especially drugs, hospitalizations and medical visits, represented the vast majority of costs, while in children, drugs, hospitalizations, medical visits, and direct non-healthcare informal costs, i.e., caregivers' time, were predominant.

A study carried out by the London School of Economics and Political Science within the BURQOL-RD project [13] identified eight costing studies, from which only three

examined labor productivity losses in addition to direct costs [14–16]. The mean annual cost per patient was estimated to be between €3471 [14] and €4663 [15], with estimates that a very small proportion of the population (12 %) is responsible for 80 % of the overall costs incurred [14].

The estimates of average annual total costs per patient ranged in our study range from €18,913 to €36,396 and are significantly higher than the reported estimates. The main reason for this difference is that, in contrast to those studies, we included costs for non-professional caregivers in the cost calculation. In our analysis, costs for non-professional care make up a substantial fraction (68.9–98.5 %) of the direct non-healthcare costs. Subtracting these costs, the direct healthcare costs calculated in our analysis still show a considerable difference compared with previous studies. In Germany, the average total costs per patient excluding costs for non-professional caregivers are €17,731, which is still significantly higher than the estimates (€4663) obtained by Minden et al. for 2008 [15]. The main difference in the results is down to differences in the medication applied and length of hospital stay. In the study by Minden et al., the proportion of patients treated with biologics was 6 %, compared to 53.73 % in the BURQOL-RD survey. In Germany, the annual costs for biologics ranged from €5,223.33 to €19,720.39 per patient, so the increasing number of patients receiving biologics therefore has a high impact on the mean total costs. The average length of hospital stay also significantly differs between the BURQOL-RD (10.79 days) and the study by Minden et al. (4.34) days [15].

Three patterns were seen when comparing structures of direct healthcare costs across the countries. First, medication costs took up the largest share in all samples. Second, in the German and Italian samples, hospitalizations made up the second largest cost fraction followed by medical visits, with the remaining fractions contributing less to the direct costs. Third, in contrast to Germany and Italy, costs for medical visits in France, Sweden, and the UK were higher than those for hospitalizations. Additionally, in the UK sample, the costs for medical tests took up a considerable share.

In the structure of the direct non-healthcare costs, two major fractions were observed for all countries: costs for main informal caregivers; and costs for the other informal caregivers, with the former being the largest. Costs for social services are the largest observed for the Swedish sample and costs for professional carers the largest for the UK. Transport costs have the smallest share in the direct non-healthcare costs.

Although in the French, German, Italian, and Swedish samples the second largest part is direct non-healthcare costs, in the UK, the cost of loss of labor productivity makes up a considerable share of the total. The UK sample contains a relatively large number of adults and in this sample, productivity losses are mainly caused by early retirement; however, due to the small study sample, it is difficult to derive a valid inference about stable causality.

A review of HRQOL instruments used for rare diseases was carried out within the BURQOL-RD project by the Swedish Institute for Health Economics (IHE) [17]. Thirty articles studied HRQOL in patients with JIA, whereof the majority (24 articles) used generic measurements, such as the Childhood Health Assessment Questionnaire (CHAQ), SF-36 or EQ-5D; with the latter two showing impairment compared to the general population [18–20]. Only four articles applied a disease-specific questionnaire, either the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) [21–23] or Arthritis Impact Measurement Scales [19].

In this study, we used a range of instruments to quantify health-related quality of life for patients with JIA and non-professional caregivers: the EQ-5D index score and the VAS scale were used to measure HRQOL in both patients and caregivers; the Barthel index was applied to patients only; and the Zarit scale was used for caregivers only.

The EQ-5D index score estimates HRQOL obtained for the patients were close to the middle of the possible range and lower than for caregivers. The estimates obtained with the VAS scale similarly showed lower values of the patients' HRQOL as those of the caregivers, supporting the results obtained using the EQ-5D index. Both instruments indicated a reduction in health status for patients with JIA. Additionally, the average Barthel index score of 91.5 implied the presence of mild dependence, however, this could be caused by inclusion of children in the calculations.

Comparison of the results among the countries indicated contrastingly low HRQOL estimates for patients in the UK sample. The population structure of this sample differed from the German and the Swedish samples, presenting older adult population of 38.5 years old on average, whereas the German and Swedish samples had younger adults with an average age of 22.8 and 24.2 years.

The resultant difference in the estimates of HRQOL might point to an age bias in average HRQOL; however, the small sample size made it difficult to provide a clear statement about a causal relationship between these variables.

Estimates of HRQOL for JIA-related non-professional caregivers indicated the existence of a caregiving burden. According to the mean Zarit score of 25.1, the burden is, on average, small. On average, the highest burden of 50.0 was reported in the French study sample, corresponding to the lowest EQ-5D utility for caregivers. The lowest burden of 16.4 was in the Italian study sample, which also corresponded to the highest EQ-5D index score estimate for caregivers.

Conclusions

The results of the BURQOL-RD project confirm the existence of socio-economic burden caused by juvenile idiopathic arthritis in Europe. Although JIA-related healthcare and non-healthcare costs vary across the countries, the estimated magnitudes of costs are high. Compared with previous studies, our results show a remarkable increase in annual healthcare costs for JIA patients. Reasons for the increase are the inclusion of non-professional caregiver costs, a wider use of biologics, and longer hospital stays. The related quality of life worsens for both patients and non-professional caregivers. Patients with JIA show a medium impairment in health status and caregivers have a life burden. The estimates of HRQOL also varied across the countries. Variation in the age structures is seen to be a possible reason for these differences.

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Compliance with ethical standards

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References

1. Ravelli, A., Martini, A.: Juvenile idiopathic arthritis. Lancet **369**(9563), 767–778 (2007). doi:10.1016/S0140-6736(07)60363-8
2. Orphanet Report Series: Prevalence of rare diseases: bibliographic data (2014)
3. Kahn, P.J.: Juvenile idiopathic arthritis—what the clinician needs to know. Bull. Hosp. Jt. Dis. **71**(3), 194–199 (2013)
4. Brooks, R.: EuroQol: the current state of play. Health policy (Amst, Neth) **37**(1), 53–72 (1996)
5. Drummond, M.F.: Methods for the economic evaluation of health care programmes, 3rd edn. Oxford medical publications, Oxford University Press, Oxford (2007)
6. McDaid, D.: Estimating the costs of informal care for people with Alzheimer's disease: methodological and practical challenges. Int. J. Geriatr. Psychiatry **16**(4), 400–405 (2001)
7. van den Berg, B., Brouwer, W.B.F., Koopmanschap, M.A.: Economic valuation of informal care. An overview of methods and applications. Eur. J. Health Econ. HEPAC Health Econo. Prev. Care **5**(1), 36–45 (2004). doi:10.1007/s10198-003-0189-y
8. Hodgson, T.A., Meiners, M.R.: Cost-of-illness methodology: a guide to current practices and procedures. Milbank Mem. Fund Q. Health Soc. **60**(3), 429–462 (1982)
9. Dolan, P.: Modeling valuations for EuroQol health states. Med. Care **35**(11), 1095–1108 (1997)
10. Mahoney, F.I., Barthel, D.W.: Functional evaluation: the Barthel index. Md. State Med. J. **14**, 61–65 (1965)
11. Shah, S., Vanclay, F., Cooper, B.: Improving the sensitivity of the Barthel index for stroke rehabilitation. J. Clin. Epidemiol. **42**(8), 703–709 (1989)
12. Hébert, R., Bravo, G., Préville, M.: Reliability, validity and reference values of the Zarit burden interview for assessing informal caregivers of community-dwelling older persons with dementia. Can. J Aging **19**(4), 494–507 (2000)
13. Angelis, A., Tordrup, D., Kanavos, P.: Socio-economic burden of rare diseases: a systematic review of cost of illness evidence. Health Policy **119**(7), 964–979 (2015)
14. Minden, K., Niewerth, M., Listing, J., Biedermann, T., Schöntube, M., Zink, A.: Burden and cost of illness in patients with juvenile idiopathic arthritis. Ann. Rheum. Dis. **63**(7), 836–842 (2004). doi:10.1136/ard.2003.008516
15. Minden, K., Niewerth, M., Listing, J., Möbius, D., Thon, A., Ganser, G., Ermisch-Omran, B., Zink, A.: The economic burden of juvenile idiopathic arthritis-results from the German paediatric rheumatologic database. Clin. Exp. Rheumatol. **27**(5), 863–869 (2009)
16. Haapasaari, J., Kautiainen, H.J., Isomäki, H.A., Hakala, M.: Etanercept does not essentially increase the total costs of the treatment of refractory juvenile idiopathic arthritis. J. Rheumatol. **31**(11), 2286–2289 (2004)
17. Ghatnekar, O., Glenngård, A., Olofsson, S., Persson, U.: A literature review of instruments for measuring health-related quality of life in rare diseases. The Swedish institute for health economics—internal report of BURQOL-RD (2011)
18. Bruns, A., Hilário, M.O.E., Jennings, F., Silva, C.A., Natour, J.: Quality of life and impact of the disease on primary caregivers of juvenile idiopathic arthritis patients. Jt. Bone Spine revue du Rhum **75**(2), 149–154 (2008). doi:10.1016/j.jbspin.2007.07.007
19. Jolles, B.M., Bogoch, E.R.: Quality of life after TKA for patients with juvenile rheumatoid arthritis. Clin. Orthop. Relat. Res. **466**(1), 167–178 (2008). doi:10.1007/s11999-007-0010-9
20. Duarte-Salazar, C., Guzmán-Vázquez, S., Soto-Molina, H., Cháidez-Rosales, P., Ilizaliturri-Sánchez, V., Nieves-Silva, J., Valero-González, F., Aguilera-Zepeda, J.M.: Disability impact on quality of life in Mexican adults with juvenile idiopathic arthritis and juvenile ankylosing spondylitis. Clin. Exp. Rheumatol. **25**(6), 922–927 (2007)
21. Amine, B., Rostom, S., Benbouazza, K., Abouqal, R., Hajjaj-Hassouni, N.: Health related quality of life survey about children and adolescents with juvenile idiopathic arthritis. Rheumatol. Int. **29**(3), 275–279 (2009). doi:10.1007/s00296-008-0672-y
22. April, K.T., Feldman, D.E., Platt, R.W., Duffy, C.M.: Comparison between Children with Juvenile Idiopathic Arthritis (JIA) and their parents concerning perceived quality of life. Qual. Life Res. **15**(4), 655–661 (2006). doi:10.1007/s11136-005-3690-1
23. Shaw, K.L., Southwood, T.R., Duffy, C.M., McDonagh, J.E.: Health-related quality of life in adolescents with juvenile idiopathic arthritis. Arthritis Rheum. **55**(2), 199–207 (2006). doi:10.1002/art.21852

Article 4

Analysis of contemporary HIV/AIDS health care costs in Germany: driving factors and distribution across antiretroviral therapy lines

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Analysis of contemporary HIV/AIDS health care costs in Germany

Driving factors and distribution across antiretroviral therapy lines

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Abstract

To analyze contemporary costs of HIV health care and the cost distribution across lines of combination antiretroviral therapy (cART). To identify variations in expenditures with patient characteristics and to identify main cost determinants. To compute cost ratios between patients with varying characteristics.

Empirical data on costs are collected in Germany within a 2-year prospective observational noninterventional multicenter study. The database contains information for 1154 HIV-infected patients from 8 medical centers.

Means and standard deviations of the total costs are estimated for each cost fraction and across cART lines and regimens. The costs are regressed against various patient characteristics using a generalized linear model. Relative costs are calculated using the resultant coefficients.

The average annual total costs (SD) per patient are €22,231.03 (8786.13) with a maximum of €83,970. cART medication is the major cost fraction (83.8%) with a mean of €18,688.62 (5289.48). The major cost-driving factors are cART regimen, CD4-T cell count, cART drug resistance, and concomitant diseases. Viral load, pathology tests, and demographics have no significant impact. Standard non-nucleoside reverse transcriptase inhibitor-based regimens induce 28% lower total costs compared with standard PI/r regimens. Resistance to 3 or more antiretroviral classes induces a significant increase in costs.

HIV treatment in Germany continues to be expensive. Majority of costs are attributable to cART. Main cost determinants are CD4-T cells count, comorbidity, genotypic antiviral resistance, and therapy regimen. Combinations of characteristics associated with higher expenditures enhance the increasing effect on the costs and induce high cost cases.

Abbreviations: ALT = alanine aminotransferase, ARV = antiretroviral, cART = combination antiretroviral therapy, CCR5 = C-C chemokine receptor type 5, CDC = Centers for Disease Control and Prevention classification system, CORSAR = Cost and

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By the fact that the patients had been receiving cART before the enrollment into the study, the selection of cART regimen in the sample was not influenced by the authors.

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Resource Utilization Study in Antiretroviral Therapy, GLM = a generalized linear model, HIV = the human immunodeficiency virus, LDL= low-density lipoprotein cholesterol, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PLWHIV = people living with HIV, SD = standard deviation.

Keywords: combination antiretroviral therapy, cost determinants, cost ratios, costs, HIV, prospective cohort survey, utilization

1. Introduction

The introduction of combined antiretroviral (ARV) therapy and its successful scale-up have resulted in major reductions in HIV-associated morbidity and mortality,[1–3] and transformed HIV into a chronic and manageable condition.[4] cART regimens have been proven effective and well tolerated, and have become the standard in HIV-related health care[4–6]; however, cART is expensive and together with the growing number of people living with HIV, who receive cART and their prolonged life expectancy, it poses an increasing financial burden on public health systems. Continuous accurate estimations of the related costs have become important for decision-making in management of HIV infection.[7] Estimates of annual total expenditures per patient have been obtained worldwide[8–13]; however, in Germany relatively few studies have investigated costs of HIV treatment since the advent of cart.[8,14–16] For the period from 2006 to 2009, mean average costs for Germany were estimated as € 23,298 per patient.[14] It has been determined that patient characteristics, such as CD4-T cell count are good predictors of annual costs; however, the authors point to a need for further research in this field.[7,14]

The objective of the present study is to explore links between costs and a wide set of patient characteristics using data, which were collected within a 96 weeks noninterventional, multicenter prospective cohort study: Cost and Resource Utilization Study in Antiretroviral Therapy (CORSAR).[16] Previously, we conducted a descriptive analysis of the cost data obtained over the first 48 weeks of this survey.[16]

In this analysis, we examine composition of the annual costs, determine major cost drivers,[17] and estimate relative cost ratios[18] between patients with varying characteristics. The relative cost ratios, in comparison to point estimates, have the advantage of possible stability across various populations, and therefore, they may be applicable to populations other than the German case.[18]

2. Methods

2.1. Setting and study design

The multicenter CORSAR study recruited patients in 8 regionally and structurally different health care providers from different areas in Germany for a prospective noninterventional survey from 2009 to 2012: 4 specialized private practices (outpatient centers) and 4 hospitals offering both HIV-related inpatient and outpatient services. The multicenter design and absence of preselection minimized a risk of bias.

Major criteria for enrolment of the patients to the survey were HIV-positive status, age older than 18 years, and ongoing cART. At the beginning of the survey, the participating sites recorded full patient data as at the date of individual entry to the study; thereafter, the observation and recording of the data were documented every 3 months on an individual schedule. The resultant database provided information on (i) demographics: age, gender, education, and income status; (ii) clinical conditions: diagnosis, time after initial diagnosis of HIV infection, CD4-T cell count, Centers for Disease Control and Prevention classification system (CDC) class, viral load, pathology tests, disability, and comorbidities; (iii) therapy: therapeutic regimen (dosage, substances, and treatment periods), line of ARV regimen at start of the study, genotypic resistance testing, and details of concomitant medications.

The following classifying parameters were assigned to the patients at the date of entry and were not changed during the follow-up period: age, CDC classification, time since the initial diagnosis of HIV before entering the study, assigned therapy regimen, and cART therapy line.

For the analysis, ARV regimens were classified according to the classes of the ARV substances (further references to the defined here ARV regimens are highlighted in Italic format and used for the purpose of the present analysis only):

1. *"NNRTI"* (non-nucleoside reverse transcriptase inhibitor): NNRTI-based regimen, consisting of 1 NNRTI in addition to nucleos(t)ide analogues;
2. "*PI-standardized*": PI-based regimen, consisting of 1 ritonavir-boosted PI (Protease inhibitor, PI/r) in addition to nucleos (t)ide analogues;
3. *"PI-individualized"*: individualized PI/r-based cART regimens consisting of elements of more than 2 different ARV classes and more than 3 different ARV substances including boosted PIs (predominantly used as a salvage regimen in multiple pretreated patients);
4. *"Other"*: other cART regimens that do not meet the criteria of the 3 previous regimen classes, that is, regimens that consist neither of PI nor NNRTI elements, that is, those based on the INSTI (integrase strand transfer inhibitor) raltegravir or the CCR5 (C-C chemokine receptor type 5) inhibitor maraviroc, nor nuke-sparing regimens, for example, boosted double PI/r therapy;
5. *"Mixed"*: if patients spent less than 95% of the year on one of the aforementioned regimen classes, their therapy classes were classified as "Mixed."

2.2. Ethical review

The CORSAR survey was approved by the national regulatory authorities and local ethics committees of all participating centers. All patients were given thorough information on the survey. Before the participation in the interviews, the patients gave a written consent. No incentive was offered for the participation in the survey.

2.3. Cost calculations

The collected data contained detailed information on utilization of various resources, including (i) cART medication and non-HIV medication; (ii) outpatient care (physicians' services, outpatient rehabilitation, nutritional, and psychological support); (iii)

inpatient care (hospital stay, inpatient costs, rehabilitation, physiotherapy, and overhead expenses); (iv) indirect costs; and (v) out-of-pocket costs.

The expenditures were calculated by taking the volume of resource utilization for inpatient days, outpatient specialist visits, lab tests, usage of in- and outpatient rehabilitation, and services of nutritionists and psychologists, and multiplying these by the respective unit cost in accordance with the current German recommendations for the assessment of health care resource consumption.[19,20] Following these recommendations,[20] we calculated drug costs taking pharmacy retail prices and subtracting manufacturer and pharmacy discounts paid to the statutory health insurance.

We estimated the unit cost of an inpatient stay based on German hospital statistics.[21] The calculation of in- and outpatient rehabilitation unit cost was performed using data from the statutory health insurance fund, retirement insurance, and the Federal Association for Rehabilitation.[22–24] Data on the unit cost for a specialist visit were retrieved from the salary report provided by the German Association of Statutory Health Insurance Doctors.[25] Publically available reports on supportive medical care were used in estimating the unit cost for massages and physiotherapy services.[26–28] Indirect costs were calculated as the product of number of days of absence from work and work compensation per day. To avoid overestimation of the indirect costs of early retirements or permanent occupational disability, we put an upper limit to the days of absence from work equal to the vacancy time of jobs in Germany in 2012 (77 days).[20] This approach is a simplification of the friction costs approach.[29]

Cumulative annual costs were calculated prospectively by annualization. Total costs were computed as the sum of the cost fractions following a bottom-up method.

2.4. Analysis

Total costs were analyzed separately for each year of the observational period. We excluded from the obtained data all individuals on treatment break, all patients who had abandoned the survey during the first year, and those patients who incurred extremely high expenditures on non-HIV medication (over €100,000/year). We defined proportions for each of the cost components and analyzed the variation of the total costs across the patient variables. We calculated means and standard deviations of the total costs as well as the costs in each fraction.

In order to estimate mean annual costs as a function of various patient characteristics, we employed different multiple regression models. We developed the models based on distributional characteristics of the cost data and selected the best-fitting model using McFadden's pseudo-R^2 and measures of prediction ability.[30] We used the obtained estimates to calculate cost ratios[18] that allowed the comparison of cost projections for patients with varying indicative characteristics while holding others unchanged. Detailed description of the model development and estimation of the cost ratios are given in Appendix A (see Appendix A and to that related Table 9, Table 10, and Figures 2–5, Supplemental Content, http://links.lww.com/MD/B55, which describe the applied methods in greater detail).

3. Results

Overall, CORSAR enrolled 1154 adult patients. In total, we excluded 132 patients: 63 people with treatment interruptions, 65 people who abandoned the survey during the first year and 4 patients who incurred extremely high expenditures on non–HIV-related medications. Eighty patients did not follow the survey into the second year. The resulting sample was of 1022 patients who had completed the first year and 942 who had completed both years of the survey, totally resulting in 1964 patient years.

Table 1 reports details on the patient data and estimates of the average annualized total costs stratified across clinical and demographic variables.

The patient data for subjects lost to follow-up during the first year of the study are given in supplement (see Table 6, Supplemental Content, http://links.lww.com/MD/B55) and show no particular differences from the rest sample. Results of the descriptive analysis of the costs do not show a considerable difference between the estimates obtained for the first and the second year as well as there were no significant differences in the cost of HIV care across the 8 health care provider sites in the survey. For the first and the second year, the mean annual total costs (SD) per patient were €22,477.57 (8809.45) with a maximum of €87,920, and €22,231.03 (8786.13) with a maximum of €83,970, respectively. cART medication was found to be the major contributor (83.8%) to the total costs with mean (SD) of €18,852.53 (5297.44) in the first and €18,688.62 (5289.48) in the second year. The second largest fraction was medication costs on treatment of comorbidities with mean values of €1499.36 (3718.50) and €1805.05 (5034.45) and for the first (6.6%) and second (8.1%) years, respectively. Expenditures on inpatient care were estimated as €1246.98 (3850.15) and €984.53 (2894.06) and contributed 5.6% and 4.4% into the total costs, respectively. Further data on costs stratified by therapy line and therapy class are given in Table 2 for both years.

Tables presenting the cost data across the 8 health care providers stratified by cost categories (see Table 7, Supplemental Content, http://links.lww.com/MD/B55) and annualized costs of HIV care by cost category for both years of CORSAR(see Table 8, Supplemental Content, http://links.lww.com/MD/B55) are given in the supplemental content.

The regression analysis was performed using the full patient data collected at the beginning of the survey and data on expenditures obtained over the following 1-year period of the CORSAR survey (n = 1022; Table 1). Patients with CD4-T count below 200 cells/mm^3 incur the highest total costs, cART medication costs, and inpatient costs compared with those for patients with less advanced cellular immunodeficiency. Table 3 reports mean (SD) total costs for each therapy line and therapy class stratified by CD4-T cell count showing the same pattern of variability of the costs for different disease stages across therapy classes and cART lines.

As assessed by 1-way analyses of variance, overall differences in mean total costs were statistically significant across the categories of the following variables: CD4-T cell count, plasma viral load of HIV, genotypic antiviral resistance, comorbidity, ARV therapy line, and therapy class.

We regressed the annual total costs against 14 explanatory variables using a generalized linear model (GLM) with a log link function and inverse Gaussian distribution of the error term.[31] The estimates with 95% confidence intervals resulting from fitting the model are given on a log scale in Table 4. Exponentiating the value of the intercept gives an estimate of the mean total costs for a hypothetical patient with the reference characteristics as €22,959.80. All estimates represent the mean differences in total costs relative to these control categories.

Table 1

Description of the CORSAR patients' data (independent variables) and respective mean annualized total costs (outcome variable; n = 1022).

Variable	Description	Categories	Percentage of observations, %	Mean total costs (SD), Euro
Patient sociodemographics				
Age group	Age group of a patient in years	20–29	2.45	20433.52 (5832.53)
		30–44	35.03	21204.40 (7139.14)
		45–59	48.43	23293.55 (9619.25)
		60+	13.99	23146.07 (9955.26)
		n.a.*	0.10	
Gender	Gender	Female	11.15	21135.21 (7313.19)
		Male	88.16	22631.30 (9001.27)
		n.a.	0.68	
Education	The highest educational level achieved	Graduated	17.22	22899.59 (9874.76)
		Neither nor	69.57	22593.78 (8792.30)
		No school certificate	1.86	22257.89 (5689.44)
		n.a.	11.35	
Income	Stable or nonstable income	Full-time employment	36.89	22109.67 (9331.49)
		Pensioner	26.22	24353.18 (9792.38)
		Other	23.48	21553.61 (7067.69)
		n.a.	13.41	
HIV-related variables				
Time since diagnosis of HIV	Time after initial diagnosis of HIV infection before entering the survey (in years)	0–10	45.89	20887.23 (6546.21)
		10–20	33.37	22856.04 (9426.28)
		>20	10.96	26947.46 (12355.37)
		n.a.	9.78	
CDC class	Class according to the CDC classification system for HIV infection	Category A: Mildly symptomatic	29.26	20444.96 (6887.97)
		Category B: Moderately symptomatic	43.25	23013.70 (8742.01)
		Category C: Severely symptomatic	27.50	23759.40 (10400.28)
		n.a.	0.00	
Viral load	HIV viral load (RNA copies/mL)	<50	85.23	22114.38 (8523.27)
		50–500	6.36	24674.51 (10423.58)
		>500	2.05	26808.55 (16209.45)
		n.a.	6.36	
CD4-T	CD4-T cell count (cells/mm^3)	>500	55.09	22014.91 (8559.18)
		200–500	38.36	22203.99 (8151.42)
		<200	6.46	27960.86 (12774.61)
		n.a.	0.10	
Treatment-related variables				
Therapy class	Assigned antiretroviral drugs classes	PI-ind	5.58	38333.72 (13250.53)
		PI-standard	40.90	25057.94 (6769.53)
		NNRTI	26.52	18221.90 (5457.26)
		Mixed	7.63	22575.21 (9796.56)
		Other	19.37	18295.04 (7014.85)
		n.a.	0.00	
Therapy line	Combination antiretroviral therapy (cART) line	First line	42.27	21182.04 (7193.05)
		Second and third line	17.03	21259.52 (7562.71)
		Beyond the third line	27.89	25285.13 (10824.55)
		n.a.	12.82	
Resistance	Genotypic resistance against antiretroviral medication	No resistance	82.58	21737.98 (8164.37)
		Three classes (PI, NNRTI, and NRTI) and more	4.31	16546.00 (4625.89)
		NNRTI	0.20	27411.45 (11468.56)
		NRTI	1.08	27876.00 (10467.59)
		NRTI and NNRTI	0.49	23194.37 (9335.68)
		PI	7.63	23491.32 (9016.87)
		PI and NRTI	3.72	32670.73 (12439.09)
		n.a.	0.00	
General health-related variables				
ALT test	Alanine aminotransferase test (U/L)	<110	94.81	22454.79 (8787.94)
		≥110	2.64	24926.26 (11215.06)
		n.a.	2.54	
LDL test	Low-density lipoprotein cholesterol test (mg/dL)	<200	76.91	22645.74 (8996.35)
		≥200	1.96	22207.95 (4438.80)

Variable	Description	Categories	Percentage of observations, %	Mean total costs (SD), Euro
		n.a.	21.14	
Creatinine test	Serum creatinine level test (mg/dL)	< 0.9	49.12	21853.01 (8385.95)
		0.9–1.5	46.67	23165.05 (8911.07)
		>1.5	1.66	28518.82 (17065.95)
		n.a.	2.54	
Comorbidity	Number of concomitant diseases and degree the severity of the severest among the diseases	≤2non-severe	33.46	21153.69 (8564.13)
		≤2 severe	8.61	24335.64 (9100.47)
		>2 nonsevere	25.05	21886.39 (7486.47)
		>2 severe	4.01	28704.37 (14693.85)
		None	28.86	21004.24 (8180.29)
		n.a.	0.00	
Disability	Disability index according to the German the Disabled Persons Act†	0—No disability	50.39	21206.26 (7834.82)
		<50—Intermediate/moderate disability	11.35	22169.72 (8152.56)
		≥50—Severe disability in activities of daily living	28.96	24762.82 (10245.40)
		n.a.	9.30	

ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention classification system; HIV = human immunodeficiency virus; LDL = low-density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

* Not available observations.

† Grad der Behinderung (GdB), Deutsches Schwerbehindertenrecht.

The results of the regression revealed that low CD4-T cell count, genotypic resistance against ARV medication, and a greater number and severity of concomitant diseases were strong predictors of more intensive health care utilization and increased treatment costs. Higher costs were induced by the following levels of the predictors: evidence of cellular immunodeficiency at entry to CORSAR ("CD4-T cell count between 200 and 500/mm^3" or "less than 200/mm^3") vs. nonimpaired immune status ("more than 500/mm^3"), disability with index ">50" versus index "0," comorbidity classified as more than 2 nonsevere concomitant diseases and more than 2 severe concomitant diseases versus control category of fewer than 2 nonsevere concomitant diseases, therapy class defined as *"PI-individualized"* versus *"PI-standardized*," drug resistance to *PI*-based regimens or to 3 or more ARV classes versus no genotypic resistance.

The following categories of the predictors were associated with lower costs relative to the control categories: female gender, "10–20 years" versus "0–10 years" after the first positive diagnosis of HIV infection, a laboratory test of blood creatinine with level of ">1.5" versus "<0.9," therapy class of *"NNRTI," "Mixed,"* and *"Other"* category versus *"PI-standardized"* category. Age, CDC-class, laboratory tests low-density lipoprotein (LDL) and alanine aminotransferase (ALT), and viral load did not appear to have a significant effect on the total costs within the study.

Using the obtained estimates, we calculated cost ratios between patients with different characteristics.[18] Assuming all other patient characteristics being held constant, cost ratios were estimated relative to the following comparison group: "male" gender, *"PI-standardized"* therapy class, "<500" CD4-T cell count, comorbidity of fewer than 2 nonsevere diseases, no drug resistance. The ratios were calculated across genders, all CD4-T cell strata, all therapy classes, and 2 categories of drug resistance: resistance to at least 3 therapy classes and no resistance. Figure 1 illustrates calculated cost ratios. The values of the ratios and respective confidence intervals are given in Table 5.

The relative costs show either increasing or decreasing effects of the selected categories of the patients characteristics on the costs in terms of factors relative to the reference case, and can be used to explore interactions among groups of the patient characteristics.

The cost ratios show an enhanced increasing effect of a combination of the patient characteristics associated with higher costs. For instance, for those with resistance to 3 or more ARV classes the costs increase by a factor of 1.266. For those with combination of this resistance with a complex individualized cART regimen, the costs increase by a factor of 1.818. Adding to this combination a low CD4-T cell count and severe comorbidity increases the costs by more significant factors: of 2.202 and 2.722, respectively.

4. Discussion

The strength of CORSAR is that it provides recent cost-of-disease data of HIV infection in a prospective, multicenter study design within a large national cohort in Germany, representing different structures of the German health care providers. It reflects the actual state of cART for patients in different stages of HIV disease and on different ARV treatment lines, including more recently approved ARVs, complies with current treatment guidelines, and takes into account actual price changes in the cART medication during the observation period. Additionally, the present work gains an advantage with estimating the cost ratios that can be applicable for other populations.

The estimated average annual total costs per patient (€22,231.03) are slightly lower comparing with the results of Mostardt et al (€23,298)[14] who conducted their study in Germany, using 2008 as the price reference year. As well as, our estimates fall into ranges of estimates provided in different studies conducted in the United States[7,32,33] and European countries.[8] Overall, comparison of the results between the studies should be done cautiously due to considerable differences in the design of the observational surveys and the resultant population samples.

The proportion of cART costs in total costs has risen from about 67% to about 84% and the fraction of inpatient care costs has decreased from the level estimated in 2001,[34] suggesting a shift of cost out of the inpatient sector to cART medication.

Table 2

Data on annual costs for patients who completed both years of the CORSAR survey (n = 942).

Cost category	Mean value (SD), Euro	Mean of total costs (SD) stratified by cARV classes (Euro)					Mean of total costs (SD) stratified by therapy line (Euro)		
		PI-ind	PI-stand	NNRTI	Mixed	Other	The first	The second and the third	Beyond the third
First year									
Total	22477.57 (8809.45)	38807.37 (13347.77)	25021.43 (6773.17)	18305.38 (5526.97)	22318.67 (9320.46)	18350.06 (7136.07)	21226.70 (7317.71)	21561.67 (7784.97)	25111.35 (10721.43)
cART drugs	18852.53 (5297.44)	31652.08 (8806.35)	21363.35 (2377.22)	15290.10 (2105.68)	17490.97 (5055.32)	15352.91 (2557.63)	18124.78 (3529.85)	17722.98 (4408.11)	21002.50 (7066.84)
non-ARV medication	1499.36 (3718.50)	2631.13 (4025.93)	1440.57 (3631.37)	1187.56 (2774.55)	1679.84 (3405.73)	1658.48 (4849.21)	1437.29 (3915.39)	1235.37 (2844.53)	1507.77 (2637.36)
Inpatient	1246.98 (3850.15)	807.01 (2465.48)	1547.97 (3917.44)	1767.41 (5269.66)	2848.24 (6271.08)	1335.85 (4034.88)	807.01 (2465.48)	1547.97 (3917.44)	1767.41 (5269.66)
Outpatient	237.04 (365.61)	411.53 (435.21)	237.66 (423.93)	221.47 (305.75)	340.76 (444.53)	174.23 (204.52)	203.80 (344.77)	292.88 (481.83)	256.26 (301.55)
Out-of-pocket	212.23 (588.61)	305.64 (402.85)	177.47 (402.19)	256.43 (847.86)	265.75 (392.49)	187.67 (611.58)	159.72 (322.66)	292.83 (821.54)	227.21 (748.75)
Indirect	1462.79 (3997.91)	3298.73 (6981.94)	1783.14 (5087.58)	922.70 (1818.29)	2072.96 (3530.65)	1063.23 (3200.57)	1502.04 (4454.53)	1575.45 (4754.07)	1414.07 (2998.35)
Second year									
Total	22231.03 (8786.13)	37160.13 (12910.61)	24996.83 (7557.19)	18473.63 (5270.54)	21371.81 (9912.31)	17720.64 (6222.37)	21375.84 (8317.12)	21530.47 (8521.24)	24142.63 (9427.27)
cART drugs	18688.62 (5289.48)	30261.38 (9128.45)	21118.57 (2857.45)	15242.47 (2075.62)	17639.52 (6054.55)	15427.86 (2778.26)	17999.36 (3822.80)	17437.05 (4467.77)	20615.94 (6863.31)
Non-ARV medication	1805.05 (5034.45)	4481.83 (8921.18)	1797.47 (5359.98)	1499.81 (3248.62)	1859.79 (5037.11)	1432.97 (4589.33)	1704.13 (5592.51)	1548.70 (4512.54)	1945.12 (4058.64)
Inpatient	984.53 (2894.06)	1205.02 (2835.33)	1257.06 (3436.72)	927.38 (2631.36)	938.43 (2913.44)	455.77 (1723.47)	969.09 (2829.57)	1530.18 (3728.38)	843.41 (2586.54)
Outpatient	240.06 (391.10)	469.14 (585.54)	239.97 (410.57)	234.36 (355.41)	350.59 (505.19)	148.92 (218.48)	200.08 (352.24)	289.60 (504.87)	287.30 (398.81)
Out-of-pocket	200.87 (605.36)	295.43 (353.03)	233.58 (820.15)	165.88 (335.26)	252.55 (546.88)	133.94 (364.22)	184.13 (776.05)	196.67 (474.20)	231.80 (449.92)
Indirect	1779.37 (4175.84)	665.39 (1004.72)	1691.89 (4897.11)	2054.83 (3487.30)	3116.64 (6525.48)	1487.30 (3175.83)	1898.57 (4975.25)	2498.60 (3682.13)	633.71 (880.17)

ARV = antiretroviral; cART = combination antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

*The estimates of the annualized total costs presented in Table 2 include also negligible cost fractions, for example, massages, psychological support, nutrition consulting.

Table 3

Mean annualized total costs (SD) by CD4-T cells count stratum, the therapy line, and the therapy class.

Mean of total costs (SD) across combination antiretroviral therapy lines stratified by CD4-Tcell count (n = 1022; Euro)			
CD4–T cells/mm^3	The first	The second and the third	Beyond the third
>500	21551.78 (8152.84)	20739.94 (7130.33)	23911.55 (10345.39)
200–500	20609.06 (5824.29)	21056.82 (7239.24)	26060.39 (10305.20)
<200	22592.92 (7701.60)	27489.64 (10824.19)	32418.55 (14193.73)

Mean of total costs (SD) across antiretroviral drugs classes stratified by CD4-T-cell count (n = 1022; Euro)					
CD4–T cells/mm^3	PI-ind	PI-stand	NNRTI	Mixed	Other
>500	37762.54 (13829.54)	25234.02 (7661.74)	17569.25 (4773.33)	20696.30 (6837.91)	17445.12 (4510.64)
200–500	37407.90 (12499.68)	24476.15 (5203.15)	18993.48 (6276.20)	21702.12 (9941.09)	18020.45 (6544.42)
<200	42763.12 (13935.73)	27503.20 (5701.21)	20455.50 (5685.62)	28441.08 (15167.92)	26177.79 (15844.88)

NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Mean cART costs are higher for first-line therapy compared with second- and third-line therapies. The difference is a consequence of the applied ARV regimens: PI/r or INSTI-based regimens were commonly used in first-line therapy and were more expensive than NNRTI-based cART regimens, which were widely applied in second- or third-line cART in Germany before 2013. The predominance of PI/r-based cART in first-line therapy has been previously described in the German Clin-Surv cohort and explained by the assumption of an elevated risk of virologic failures and selection for viral resistance by NNRTIs in cART-naïve patients with a high viral load.[34]

Table 4

Summary of the regression analysis for annualized total costs (GLM with inverse Gaussian distribution of the error term and log link function; n = 1022).

Predictor/reference category	Comparative category	Estimate	Upper CI 95%	Lower CI 95%	$P>\|t\|$
Intercept		10.0415***	10.1278	9.9553	<0.001
Age group/45–59	20–29	−0.0925	0.0716	−0.2567	0.2698
	30–44	−0.0012	0.0510	−0.0533	0.9647
	60+	0.0140	0.0898	−0.0618	0.7177
Gender/male	Female	−0.0891*	−0.0170	−0.1611	0.0157
Disability/none (index "0")	"< 50"	0.0517	0.1216	−0.0182	0.1479
	"≥ 50"	0.0795**	0.1351	0.0239	0.0053
CDC class/B	A	−0.0398	0.0149	−0.0945	0.1540
	C	−0.0545	0.0053	−0.1143	0.0747
Therapy line/the first line	Beyond the third	0.0334	0.0954	−0.0287	0.2926
	The second and the third	0.0555	0.1212	−0.0102	0.0984
Lab ALT/< 110	≥110	−0.0712	0.0683	−0.2107	0.3178
Lab CREAT/<0.9	> 1.5	−0.2205*	−0.0435	−0.3975	0.0150
	0.9–1.5	−0.0119	0.0370	−0.0609	0.6335
Lab LDL/<200	≥ 200	−0.0150	0.1517	−0.1818	0.8598
Comorbidity/≤2 nonsevere	≤2 severe	0.0364	0.1194	−0.0466	0.3902
	>2 nonsevere	0.0785*	0.1404	0.0165	0.0134
	>2 severe	0.2119***	0.3345	0.0892	0.0008
	None	0.0381	0.0990	−0.0228	0.2204
Viral load/<50	> 500	0.0995	0.2895	−0.0905	0.3051
	50–500	−0.0196	0.0810	−0.1203	0.7023
CD4-T cells count/>500	200	0.1917***	0.3017	0.0816	0.0007
	200–500	0.0474	0.0969	−0.0022	0.0615
Time since diagnosis/0–10 years	10–20 years	−0.0573*	−0.0004	−0.1143	0.0491
	>20 years	0.0816	0.1706	−0.0073	0.0728
Drug resistance/none	Three classes (NNRTI, PI, NRTI)	0.2359***	0.3743	0.0975	0.0009
	NNRTI	−0.0711	0.4326	−0.5748	0.7820
	NRTI	0.0523	0.3056	−0.2009	0.6855
	NRTI and NNRTI	0.2837	0.7547	−0.1873	0.2383
	PI	0.0742	0.1546	−0.0062	0.0710
	PI and NRTI	0.0048	0.1186	−0.1089	0.9335
Therapy class/PI-stand	PI-indiv	0.3620***	0.5019	0.2220	<0.001
	NNRTI	−0.3239***	−0.2643	−0.3835	<0.001
	Mixed	−0.1849***	−0.0857	−0.2841	<0.001
	Other	−0.3079***	−0.2462	−0.3695	<0.001

ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention classification system; LDL = low-density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
Signif. codes: 0; "***", 0.001; "**", 0.01; "*", 0.05; ".", 0.1; " ", 1.

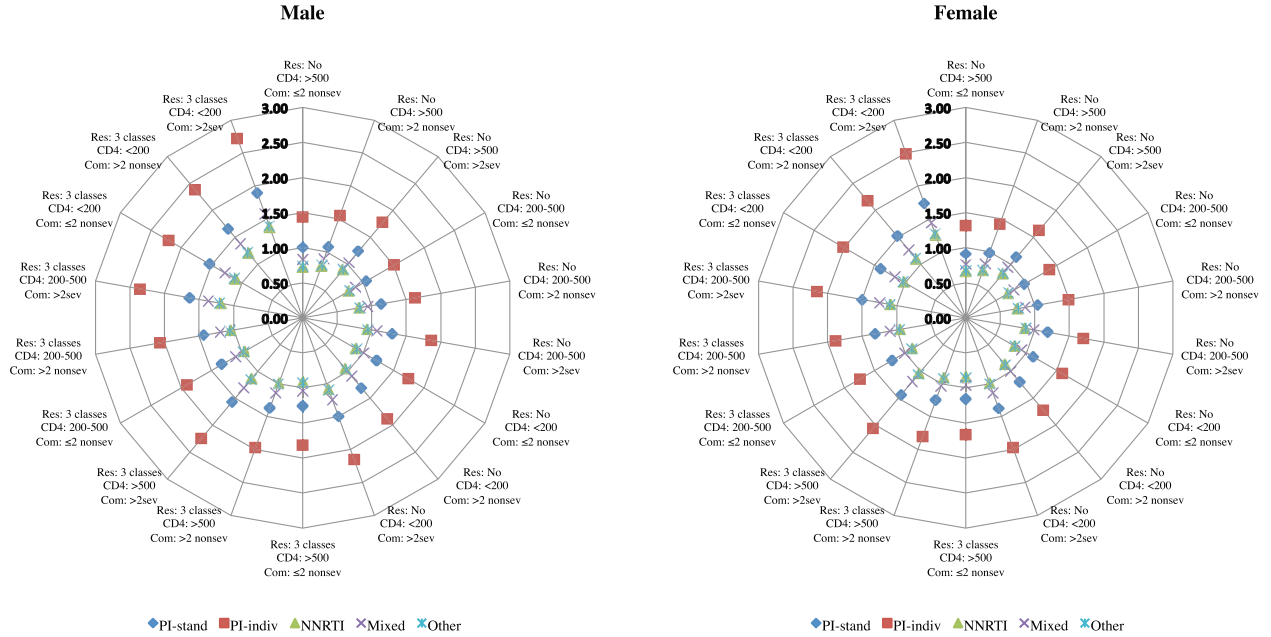

Figure 1. Spider web plot of cost ratios between patients with varying characteristics. Points on the axis give either increasing or decreasing effects of the presented groups of patient characteristics relative to the reference case for men (left) and women (right). Point types represent the respective therapy classes. The blue rhombus in the middle of the plot (left) gives the reference case, which corresponds to a cost ratio of 1 and the following characteristics: male, therapy class = "PI-stand," CD4 = ">500," comorbidity = "≤2 nonsevere," drug resistance = "no resistance." All other ratios (including those given on the plot for women) are presented relative to the reference case. *Res*, drug resistance; *CD4*, CD4-T cells count group; *Com*, comorbidity (categories are described in Table 1).

The second- and third-line therapies, however, are associated with higher utilization of nonmedication HIV care: hospital stays, outpatient care, and rehabilitation. Higher health care services consumption is mainly caused by occurrence of intercurrent diseases or immune reconstitution inflammatory diseases among late-presenting patients with HIV in the first years after initiation of cart.[35,36] Patients under therapy beyond the third-line report the highest direct costs for cART medication, these being driven by more complex ARV treatment regimens: a higher amount of used substances and increased doses of certain ARVs. Although it was not documented in CORSAR, it is reasonable to suggest that switching to a beyond the third-line therapy might be induced either by treatment failures or strategic aspects of ARV treatment or by an intention to overcome adverse long-term effects or individual intolerances against certain ARVs.

The modeling methods applied in this study reveal possible determinants of the average annual costs per patient. Mean total costs increase with a decline in CD4-T cell count. This result is consistent with findings of other studies[7,14]; however, when considering the clinical stage, CDC classification variable, particularly class C, which defines the AIDS stage, shows an absence of statistically significant estimates. It suggests that long-term surviving the AIDS stage does not impact on annual costs; thus, only actual CD4-T cell count below 200/mm^3 is a strong predictor of higher costs due to the higher risk of related infections and diseases. This observation might be relevant to 3 different patient subgroups in the CORSAR cohort: (i) late presenters with advanced cellular immunodeficiency who recently started cART, (ii) patients with an immunological or clinical failing of cART, and (iii) immunological long-term nonresponders, usually late presenters, who started cART with a profound cellular immunodeficiency with a CD4-T cell count below 50/mm^3. All 3 subgroups have a higher risk of receiving a more advanced cART treatment line or to have intercurrent or concomitant diseases or both. In contrast to these subgroups, those late presenters who have been receiving cART for more than 1 or 2 decades and belong to the CDC-C class, but have actual CD4-T cell counts within the normal range, are more likely to receive less complex cART or to have no active concomitant diseases. Female patients incur fewer costs than male patients. These differences have been previously reported elsewhere.[14,37–39] One might hypothesize a number of reasons for gender-specific differences in costs[14]; in our study, considerable differences lie in expenditures on non–HIV-related medication and indirect costs.

We also found an association between costs and the presence of concomitant diseases and disability. The source of these increasing total costs is expenditures on non-HIV medication and additional care. According to the estimated cost ratios, worsening of comorbidity, in terms of number of diseases and their severity, induces a considerable rise in annual total costs. In the CORSAR database, the reported concomitant diseases are grouped into: cardiovascular, respiratory, gastrointestinal, endocrine, neurological, psychiatric, dermatological, hematological, and allergological diseases. Defining cost variation across types of concomitant diseases requires additional data and further analysis.

With regard to the therapy-related predictors, the total costs are linked to the cART regimens, costs of which are directly related to drug prices and the number of ARVs used; when holding all other factors constant, variation of the therapy class from *PI/r*-based cART to *NNRTI*-based treatment which is available as a less expensive alternative in Germany[40] decreases annual costs in the CORSAR cohort. However, individual risks of treatment failure, development of drug resistance or occurrence of toxicity are not modeled in this study; therefore, the impact of these events on the resulting costs in long term cannot be defined. Additionally, the total costs increase when drug

Table 5

Estimated cost ratios relative to the comparison group (male individuals with therapy class "PI-stand," CD4="$>$500," comorbidity="$\leq$2 nonsevere," and drug resistance="no resistance"), 95% confidence intervals in parentheses.

Patient characteristics	Comorbidity	PI-stand	PI-indiv	NNRTI	Mixed	Other
Male. No resistance. CD4: $>$500	$\leq$2 nonsevere	1.000*	1.436 (1.249,1.652)	0.723 (0.681,0.767)	0.831 (0.753,0.918)	0.735 (0.691,0.781)
	$>$2 nonsevere	1.082 (1.016,1.151)	1.553 (1.330,1.814)	0.782 (0.471,1.230)	0.899 (0.798,1.012)	0.795 (0.730,0.865)
	$>$2 severe	1.236 (1.093,1.397)	1.775 (1.466,2.148)	0.894 (0.778,1.027)	1.027 (0.874,1.207)	0.908 (0.793,1.034)
Male. No resistance. CD4: 200–500	$\leq$2 nonsevere	1.049 (0.998,1.102)	1.506 (1.301,1.743)	0.758 (0.703,0.817)	0.871 (0.781,0.972)	0.771 (0.713,0.833)
	$>$2 nonsevere	1.134 (1.045,1.231)	1.629 (1.384,1.916)	0.820 (0.742,0.907)	0.943 (0.829,1.072)	0.834 (0.754,0.921)
	$>$2 severe	1.296 (1.133,1.482)	1.861 (1.528,2.267)	0.937 (0.808,1.087)	1.077 (0.909,1.276)	0.953 (0.824,1.102)
Male. No resistance. CD4: $<$ 200	$\leq$2 nonsevere	1.211 (1.085,1.350)	1.740 (1.461,2.071)	0.876 (0.772,0.994)	1.007 (0.872,1.162)	0.890 (0.788,1.006)
	$>$2 nonsevere	1.310 (1.151,1.491)	1.882 (1.557,2.273)	0.948 (0.821,1.094)	1.089 (0.928,1.278)	0.963 (0.838,1.106)
	$>$2 severe	1.497 (1.273,1.760)	2.150 (1.734,2.665)	1.083 (0.909,1.290)	1.244 (1.032,1.501)	1.100 (0.930,1.302)
Male. Resistance: Three classes. CD4: $>$500	$\leq$2 nonsevere	1.266 (1.102,1.454)	1.818 (1.130,2.926)	0.916 (0.574,1.461)	1.052 (0.656,1.687)	0.931 (0.583,1.485)
	$>$2 nonsevere	1.369 (1.176,1.594)	1.967 (1.624,2.382)	0.991 (0.838,1.171)	1.138 (0.951,1.363)	1.007 (0.853,1.188)
	$>$2 severe	1.565 (1.304,1.877)	2.247 (1.806,2.796)	1.132 (0.930,1.377)	1.301 (1.056,1.601)	1.150 (0.867,1.276)
Male. Resistance: Three classes. CD4:200–500	$\leq$2 nonsevere	1.327 (1.148,1.535)	1.906 (1.588,2.289)	0.960 (0.818,1.126)	1.103 (0.928,1.311)	0.976 (0.831,1.145)
	$>$2 nonsevere	1.436 (1.224,1.685)	2.062 (1.694,2.509)	1.039 (0.873,1.235)	1.193 (0.991,1.437)	1.055 (0.888,1.254)
	$>$2 severe	1.641 (1.358,1.982)	2.356 (1.885,2.945)	1.187 (0.970,1.452)	1.364 (1.102,1.687)	1.206 (0.988,1.472)
Male. Resistance: Three classes. CD4: $<$200	$\leq$2 nonsevere	1.533 (1.284,1.831)	2.202 (1.790,2.709)	1.109 (0.917,1.342)	1.275 (1.046,1.553)	1.127 (0.935,1.359)
	$>$2 nonsevere	1.659 (1.371,2.006)	2.382 (1.912,2.968)	1.200 (0.979,1.470)	1.379 (1.117,1.701)	1.219 (0.999,1.487)
	$>$2 severe	1.895 (1.535,2.340)	2.722 (2.141,3.461)	1.371 (1.096,1.714)	1.575 (1.243,1.997)	1.393 (1.120,1.732)
Female. No resistance. CD4: $>$500	$\leq$2 nonsevere	0.915 (0.851,0.983)	1.314 (1.123,1.537)	0.662 (0.601,0.729)	0.760 (0.674,0.858)	0.672 (0.609,0.741)
	$>$2 nonsevere	0.989 (0.901,1.086)	1.421 (1.199,1.684)	0.716 (0.638,0.803)	0.822 (0.718,0.942)	0.727 (0.649,0.814)
	$>$2 severe	1.131 (0.984,1.298)	1.624 (1.328,1.985)	0.818 (0.700,0.955)	0.940 (0.791,1.116)	0.831 (0.714,0.967)
Female. No resistance. CD4: 200–500	$\leq$2 nonsevere	0.959 (0.877,1.048)	1.377 (1.169,1.622)	0.694 (0.622,0.773)	0.797 (0.670,0.908)	0.705 (0.631,0.787)
	$>$2 nonsevere	1.037 (0.930,1.157)	1.490 (1.248,1.779)	0.750 (0.661,0.851)	0.862 (0.745,0.998)	0.763 (0.673,0.864)
	$>$2 severe	1.185 (1.020,1.377)	1.703 (1.381,2.096)	0.857 (0.727,1.011)	0.985 (0.822,1.180)	0.871 (0.741,1.024)
Female. No resistance. CD4: $<$200	$\leq$2 nonsevere	1.108 (0.973,1.262)	1.591 (1.319,1.919)	0.801 (0.692,0.928)	0.921 (0.786,1.078)	0.814 (0.706,0.939)
	$>$2 nonsevere	1.199 (1.035,1.386)	1.721 (1.409,2.103)	0.867 (0.738,1.018)	0.996 (0.838,1.183)	0.881 (0.754,1.029)
	$>$2 severe	1.370 (1.152,1.628)	1.967 (1.573,2.458)	0.991 (0.821,1.194)	1.138 (0.934,1.387)	1.007 (0.840,1.206)
Female. Resistance: Three classes. CD4: $>$500	$\leq$2 nonsevere	1.158 (0.990,1.354)	1.663 (1.372,2.016)	0.838 (0.705,0.995)	0.963 (0.803,1.154)	0.851 (0.716,1.011)
	$>$2 nonsevere	1.253 (1.059,1.481)	1.799 (1.467,2.205)	0.906 (0.754,1.088)	1.041 (0.858,1.262)	0.921 (0.768,1.104)
	$>$2 severe	1.431 (1.180,1.736)	2.056 (1.637,2.581)	1.035 (0.841,1.275)	1.190 (0.958,1.477)	1.052 (0.857,1.291)
Female. Resistance: Three classes. CD4: 200–500	$\leq$2 nonsevere	1.214 (1.031,1.429)	1.744 (1.432,2.123)	0.878 (0.735,1.049)	1.009 (0.837,1.216)	0.893 (0.747,1.066)
	$>$2 nonsevere	1.313 (1.102,1.565)	1.886 (1.531,2.324)	0.950 (0.786,1.148)	1.092 (0.895,1.331)	0.965 (0.799,1.165)
	$>$2 severe	1.501 (1.228,1.834)	2.155 (1.708,2.719)	1.086 (0.876,1.344)	1.247 (0.998,1.557)	1.103 (0.893,1.362)
Female. Resistance: Three classes. CD4: $<$200	$\leq$2 nonsevere	1.403 (1.117,1.761)	2.015 (1.566,2.591)	1.015 (0.798,1.289)	1.166 (0.914,1.486)	1.031 (0.813,1.306)
	$>$2 nonsevere	1.517 (1.196,1.924)	2.179 (1.677, 2.831)	1.098 (0.966, 1.246)	1.261 (0.977,1.627)	1.115 (0.872,1.425)
	$>$2 severe	1.734 (1.346,2.232)	2.490 (1.886,3.286)	1.254 (0.962,1.634)	1.441 (1.101,1.885)	1.274 (0.982,1.653)

NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

* The cell with a cost ratio of 1 indicates reference categories: all other ratios are estimated relative to them.

resistance occurs; average total costs are particularly responsive to genotypic *PI*-resistance and resistance to 3 or more ARV classes, respectively. One of the results of the regression is that kidney insufficiency (creatinine $>$1.5 vs. $<$0.9) decreases total costs, which is opposite to our expectations; however, the small number of observations in this category (1.66%) prevents a possibility to provide this inference for the whole population.

Viral load is not identified as a cost determinant. Although a link between occurrence of detectable viremia and an increase of annual costs would be suggestive, the design of the CORSAR might not be capable of observing such an effect: (i) the 2-year observation period of the survey might be too short, (ii) the proportion of viremic patients is rather small, and (iii) most cases have either a singular viremic "blip," low viremia, or both, which are associated with a low risk for subsequent virological failure or short-term progression of HIV infection. Further studies with a longer observational period and a rather more restrictive definition of viremic patients will be necessary to investigate the long-term effects of HIV viremia in cART-treated patients on the costs of HIV therapy.

The calculated cost ratios can be interpreted in a similar way as the odd ratios estimated from proportional hazard models.[18] Using relative costs, one can explore interactions among the patients, for example, compare relative costs between patients with varying characteristics. Particularly, combination of a low CD4-T cell count, multiple resistance against *PI* or more than 1 ARV class, severe comorbidity leads to high cost cases. Table 5 and Figure 1 bring additional information and could be useful particularly to health care payers. Some of these cases might be prevented with improvement of ARV adherence, that is by a

patient's ability to follow a prescribed cART plan in accordance with the time lines.[41,42,43]

Our study has certain limitations. First, as a consequence of the selection criteria, ARV-naïve patients were excluded from the study and costs were calculated exclusively for patients under ARV therapy. Therefore, we cannot provide inferences on the costs of ARV-naïve patients or those without cART. Second, information on transmission risks is not available in all participating centers and, therefore, not analyzed. In conclusion, the annual total costs per patient of HIV-related health care in Germany continue to be high and vary greatly depending on severity of the infection, comorbidity, and treatment attributes of patients. The cost ratios and respective confidence intervals show considerable variation within the stratum of CD4-T cell count, genotypic resistance, and ARV classes. The high-cost cases are induced by combinations of low CD4-T cell counts, resistance to at least 3 ARVs and *individualized PI*-based therapy. Improvement of adherence as well as development of cART regimens with enhanced forgiveness (the ability of ARV to sustain viral suppression, despite insufficient adherence) may prevent occurrence of a part of high cost cases of HIV treatment and, therefore, they should be seen as major objectives in management of HIV infection.

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References

[1] Jaggy C, Overbeck F von, Ledergerber B, et al. Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. Lancet 2003;362:877–8.
[2] Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One 2013;8:e81355.
[3] Helleberg M, May MT, Ingle SM, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. AIDS 2015;29:221–9.
[4] Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (November 13, 2014). Retrieved from http://aidsinfo.nih.gov/ContentFiles/Adultand.
[5] World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. Geneva: World Health Organization; 2013.
[6] Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. J Am Med Associat 2014;312:410–25.
[7] Gebo KA, Fleishman JA, Conviser R, et al. Contemporary costs of HIV healthcare in the HAART era. AIDS 2010;24:2705–15.
[8] Trapero-Bertran M, Oliva-Moreno J. Economic impact of HIV/AIDS: a systematic review in five European countries. Health Econ Rev 2014;4:15.
[9] Beck EJ, Harling G, Gerbase S, et al. The cost of treatment and care for people living with HIV infection: implications of published studies, 1999–2008. Curr Opin HIV AIDS 2010;5:215–24.
[10] Levy AR, James D, Johnston KM, et al. The direct costs of HIV/AIDS care. Lancet Infect Dis 2006;6:171–7.
[11] Yazdanpanah Y, Goldie SJ, Losina E, et al. Lifetime cost of HIV care in France during the era of highly active antiretroviral therapy. Antivir Ther 2002;7:257–66.
[12] Sloan CE, Champenois K, Choisy P, et al. Newer drugs and earlier treatment: impact on lifetime cost of care for HIV-infected adults. AIDS 2012;26:45–56.
[13] Gazzard B, Moecklinghoff C, Hill A. New strategies for lowering the costs of antiretroviral treatment and care for people with HIV/AIDS in the United Kingdom. Clinicoecon Outcomes Res 2012;4:193–200.
[14] Mostardt S, Hanhoff N, Wasem J, et al. Cost of HIV and determinants of health care costs in HIV-positive patients in Germany: results of the DAGNÄ K3A Study. Eur J Health Econo 2013;14:799–808.
[15] Hoeper K, Stoll M, Schmidt RE, et al. Langzeitauswirkungen auf gesundheitsökonomische Folgekosten im Jahr 2010 durch den initialen antiretroviralen Therapiebeginn bei HIV-Patienten. Gesundheitswesen 2011;73.
[16] Kuhlmann A, Mittendorf T, Hower M, et al. Krankheitskosten von HIV-Patienten unter antiretroviraler Therapie in Deutschland – Ergebnisse einer 48-Wochen-Interimsanalyse im Rahmen der prospektiven multizentrischen Kohortenstudie 'CORSAR'. Cost of Illness of HIV Patients under Anteretroviral Therapy in Germany – Results of the 48-Week Interim Analysis of the Prospective Multicentre Observational Study 'CORSAR'. Gesundheitswesen 2014.
[17] Mihaylova B, Briggs A, O'Hagan A, et al. Review of statistical methods for analysing healthcare resources and costs. Health Econ 2011;20:897–916.
[18] Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. Health Services and Outcomes Research Methodology 2000;1:185–202.
[19] Braun S, Prenzler A, Mittendorf T, et al. Bewertung von Ressourcenverbräuchen im deutschen Gesundheitswesen aus Sicht der Gesetzlichen Krankenversicherung. Gesundheitswesen 2009;71:19–23.
[20] Prenzler A, Zeidler J, Braun S, et al. Bewertung von Ressourcen im Gesundheitswesen aus der Perspektive der deutschen Sozialversicherung. PharmacoEconomics German Research Articles 2010;8:47–66.
[21] Deutsches Statistisches Bundesamt. Krankenhausfälle, Krankenhaustage und Tage je Fall der Versicherten der gesetzlichen Krankenversicherung. Retrieved from http://www.gbe-bund.de.
[22] Deutsche Rentenversicherung Bund. Reha-Bericht 2012. Retrieved from http://www.deutsche-rentenversicherung.de/cae/servlet/contentblob/235592/publicationFile/30904/rehabericht_2012.pdf.
[23] Bundesministerium für Gesundheit. Ergebnisse der Statistik KG 5, Vorsorge- und Rehabilitationsmaßnahmen der Gesetzlichen Krankenversicherungen. Retrieved from http://www.bmg.bund.de/fileadmin/dateien/Downloads/Statistiken/GKV/Geschaeftsergebnisse/120705_Ergebnisse_der_Statistik_KG_5__Vorsorge-_und_Rehabilitationsmassnahmen.pdf.
[24] Bundesarbeitsgemeinschaft für Rehabilitation. Statistik der Ausgaben für Rehabilitation und Teilhabe 2008-2010. Retrieved from http://www.bar-frankfurt.de/fileadmin/dateiliste/rehabilitation_und_teilhabe/DatenundFakten/downloads/Statistiktabelle_2008_2010.pdf.
[25] Kassenärztliche Bundesvereinigung. Kennzahlen der Abrechnungsgruppen 1. Quartal 2009 bis 1. Quartal 2012. Retrieved from https://www.kbv.de/41532.html.
[26] Claudia Kemper, Kristin Sauer, Gerd Glaeske. BARMER GEK Heil- und Hilfsmittel-Report 2011. Retrieved from https://presse.barmer-gek.de/barmer/web/Portale/Presseportal/Subportal/Infothek/Studien-und-Reports/Heil-und-Hilfsmittelreport/Einstieg-HeHi-Reports.html.
[27] Claudia Kemper, Kristin Sauer, Gerd Glaeske. BARMER GEK Heil- und Hilfsmittel-Report 2012. Retrieved from https://presse.barmer-gek.de/barmer/web/Portale/Presseportal/Subportal/Infothek/Studien-und-Reports/Heil-und-Hilfsmittelreport/Einstieg-HeHi-Reports.html.
[28] Kristin Sauer, Claudia Kemper, Kathrin Kaboth. BARMER GEK Heil- und Hilfsmittel-Report 2010. Retrieved from https://presse.barmer-gek.de/barmer/web/Portale/Presseportal/Subportal/Infothek/Studien-und-Reports/Heil-und-Hilfsmittelreport/Einstieg-HeHi-Reports.htm.
[29] Koopmanschap MA, Rutten FF, van Ineveld BM, et al. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14:171–89.
[30] Austin PC, Ghali WA, Tu JV. A comparison of several regression models for analysing cost of CABG surgery. Stat Med 2003;22:2799–815.
[31] Manning WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ 2001;20:461–94.
[32] Schackman B, Fleishman J, Su A, et al. The lifetime medical cost savings from preventing HIV in the United States. Med Care 2015;53:293–301.
[33] Leibowitz A, Desmond K. Identifying a sample of HIV-positive beneficiaries from medicaid claims data and estimating their treatment costs. Am J Public Health 2015;105:567–74.
[34] Stoll M, Kollan C, Bergmann F, et al. Calculation of direct antiretroviral treatment costs and potential cost savings by using generics in the German HIV ClinSurv cohort. PLoS One 2011;6:e23946.

[35] Krentz HB, Gill MJ. The Direct Medical Costs of Late Presentation. AIDS Res Treat 2012;1–8.
[36] Miro JM, Manzardo C, Mussini C, et al. Survival outcomes and effect of early vs. Deferred cART among HIV-infected patients diagnosed at the time of an AIDS-defining event: a cohort analysis. PLoS One 2011;6: e26009.
[37] Clark R. Sex differences in antiretroviral therapy-associated intolerance and adverse events. Drug Safety 2005;28:1075–83.
[38] Hellinger FJ, Fleishman JA. Estimating the national cost of treating people with HIV disease: patient, payer, and provider data. J Acquir Immune Defic Syndr 2000;24:182–8.
[39] Raveis VH, Siegel K, Gorey E. Factors associated with HIV-infected women's delay in seeking medical care. AIDS Care 1998;10:549–62.
[40] Ruof J, Schwartz FW, von der Schulenburg JM, et al. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. Eur J Health Econ 2014;15:577–89.
[41] García de Olalla P, Knobel H, Carmona A, et al. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr 2002;30:105–10.
[42] Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Int Med 2000;133:21–30.
[43] Gardner EM, Burman WJ, Steiner JF, et al. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. AIDS 2009;23:1035–46.

Appendix A.

Methods: Development of a multiple regression model.

To fulfill the aim of determining the driving factors of HIV treatment costs, multiple regression models were employed.

In order to specify relevant candidate predictors for the model, first, the number of observations and the number of missing observations for each category of each potential predictor were calculated (Table 1 in the main text).

We found that levels "*NNRTI*" and "*Mixed*" of predictor "resistance" had a small sample size. However, there was no possible method based on medical reasoning to combine the categories, and the predictor was included in the model without modifications; therefore, the coefficient estimates for these categories must be interpreted with caution.

Variance inflation factor (VIF) was used to assess potential multicollinearity among the predictors. Perfect collinearity took place between two variables that describe comorbidity: number of diseases and their severity at the level of "none." To avoid the impact of this collinearity on the model, these variables were combined into one variable that describes comorbidity in terms of both severity and number of diseases. The severity variable in this case described the severity of the severest among the diseases. With this modification, VIF analysis showed acceptable results and all variables were considered as candidate predictors.

***Variable selection*.**

Thereafter, statistical significance of each covariate was compared using *F*-tests and applying the classical ANOVA analysis of a linear model. For all analyses, statistical significance was determined at $p < 0.05$.

Further, a backward stepwise variable selection procedure was performed. The selection began with a saturated model that included all effects of interest as well as all first, second, and third-factor interactions between covariates. All variables and interactions were extracted from the model stepwise, while conclusions on the selection of variables or interactions were based on the Akaike information criterion(AIC) and residual deviance.

No interactions between predictors showed statistical significance, therefore, a simple additive model was adopted. Those predictors that showed no statistical significance but added statistical power were included in the model.

Additionally, we used regression subset selection and considered possible subsets of the pool of the predictors and compared these using AIC.

When selecting candidate predictors we considered variables that were predetermined to be included based on previous research and theoretical interest to explore the links between these variables and total costs, as well as using the statistical methods described above. The resulting system was specified as an additive model with 14 explanatory variables: age group, gender, time since diagnosis of HIV group, CDC classification, therapy class, therapy line, drug resistance, viral load, CD4-T cell count, laboratory alanine aminotransferase test(Lab ALT), laboratory low-density lipoprotein cholesterol test (Lab LDL), laboratory serum creatinine level test (Lab Creat), comorbidity, and disability.

First, a classic linear model was employed to analyze the relationship between mean total costs and patient characteristics. The Breuch Pagan test was applied to check formally for the presence of heteroscedasticity in the linear model. A positive result (p=0.00404) rejected the null hypothesis of constant variance, therefore, in the further analysis the following models were used: an OLS of log transformed costs and generalized linear models with a log link function and an exponential family of the error term.

Distributional characteristics of cost data.

In order to develop a regression model, distributional characteristics of the data on total costs were initially investigated as follows: (i) a histogram of the total costs was plotted, (ii) values of skewness and kurtoses were computed, (iii) the Shapiro-Wilk test was used to investigate whether the log transformation yielded normalization, (iv) quintile-quintile plots were used to compare the cost distributions and theoretical distributions: lognormal, gamma and inverse Gaussian, (v) mean-variance relationships were plotted, with means and variances of the total costs being computed within each level of each variable and a plot of the variance versus the mean being built [18]. R statistical software (version 3.1.1) was used.

For the selected patients (n=1022) a histogram of the annual total costs is given by Figure 2 (Appendix A). The histogram shows distributional characteristics of the total costs data.

It can be seen that the distribution is skewed to the right, which is common for data on expenditures in healthcare. The numerical measure of skewness of the present data took a value of 2.27 and that of kurtosis was 10.66. Both measures indicated a substantial positive skewness. Log transformation of the total costs data did not yield a normal distribution (Shapiro-Wilk W-test: W = 0.7963, p < 2.2e-16), however, the values of skewness (0.86) and kurtosis (4.34) were altered.

For the further investigation of the distributional characteristics of the total costs, quintile-quintile (Q-Q) plots were built. Figure 3(Appendix A) shows plots of the total costs against three selected theoretical distributions, in particular, gamma distribution with *shape* parameter = 6.489 and *scale* parameter = 3465.14; inverse Gaussian distribution with mean(*mu*) = 22485.97 and *lambda* = 145915.7, where $Var = mu^3 / lambda$; and lognormal distribution with parameters *meanlog*= 10.021 and *sdlog* = 0.337. According to the plots, total costs were best approximated by the inverse Gaussian distribution.

As long as a log transformation of the dependent variable did not normalize its distribution, the relationship between its mean and variance was analyzed. The values of these quintiles were calculated for each category of each variable. The following Figure 4(Appendix A) illustrates the mean-variance relationship on the log scale. The line was fit employing weighted least squares using degrees of freedom associated with each variance as weights [19]. The resulting slope takes a value of approximately 2.94, supporting the initial preference for the inverse Gaussian family (variance = mean^3)

Regression model.

The resulting model was specified as follows:

Denotation: Age group: *a = 1,2,3,4*; Gender: *b = 1,2;* Time since diagnosis of HIV(HIVtime): *c = 1,2,3;* CDC- classification: *d =1,2,3;* Therapy class: *h=1,2,3,4,5;* Therapy line: *i = 1,2,3;* Drug resistance: *j= 1,2,3,4,5,6,7*; Viral load: *k=1,2,3*; CD4-T cells count: *l= 1,2,3*;Lab ALT: *m=1,2*; Lab LDL: *n=1,2*; Lab Creat: *p=1,2,3*; Comorbidity: *r=1,2,3,4,5*; Disability: *v= 1,2,3.*

Let $\mu_{a,b,c,d,h,i,j,k,l,m,n,p,r,v}$ denote the mean total costs for individuals of the *a*th age group and the *b*th gender who have clinical characteristics *c, d, h, i, j, k, l, m, n, p, r, v* as denoted above, then the model can be expressed as:

$$\log(\mu_{abcdhijklmnprv}) = \beta_0 + \text{Age Group}_a + \text{Gender}_b + \text{Disability}_v + \text{CDC}_d + \text{TherapyLine}_i + \text{ALT}_m + \text{Creat}_p + \text{LDL}_n + \text{Comorbidity}_r + \text{VirLoad}_k + \text{CD4}_l + \text{HIVtime}_c + \text{Resistance}_j + \text{TherapyClass}_h$$

where β_0 is a constant, $Age\ Group_a$ is the effect due to the *a*th age group, $Gender_b$ is the effect due to the *b*th gender group, $Disability_v$ is the effect due to the *v*th disability degree, CDC_d is the effect due to the *d*th class according to the CDC-classification for HIV infection, $TherapyLine_i$ is the effect due to the *i*th therapy line, ALT_m is the effect due to the *m*thgroup of alanine aminotransferase test results, $Creat_p$ is the effect due to the *p*thgroup of laboratory serum creatinine testresults, LDL_n is the effect due to the *n*th group of laboratory low-density lipoprotein cholesterol test results, $Comorbidity_r$ is the effect due to the *r*th number of diseases and severity indexgroup, $VirLoad_k$ is the effect due to the *k*th viral load group, $HIVtime_c$ is the effect due to the *c*thtime after initial diagnosis of HIV infection before entering the survey (in years) group, $CD4_l$ is the effect due to the *l*th CD4-T cellcount group, $Resistance_j$ is the effect due to the *j*thgenotypic antiretroviralresistance group, and $TherapyClass_h$ is the effect due to the *h*thARV class.

Before fitting the given GLMs, reference categories for each predictor were specified. If previous literature or knowledge allowed us to make a specific hypothesis we used these planned contrasts in the model. Otherwise reference categories were defined for each predictor as the factor level with the largest number of observations among other levels for the respective predictor (see Table 1).All categorical variables were coded using dummy coding so that each level of factor was compared with the mean of the reference category.

The contrasts in the resulting model were specified as follows:

$$\log(\mu_{abcdhijklmnprv}) = \beta_0 + \text{Age Group}_{\text{"45-59"}} + \text{Gender}_{\text{"male"}} + \text{Disability}_{\text{"none"}} + \text{CDC}_{\text{"B"}} + \text{TherapyLine}_{\text{"1st"}} + \text{ALT}_{\text{"<110"}} + \text{Creat}_{\text{"<0.9"}} + \text{LDL}_{\text{"<200"}} + \text{Comorbidity}_{\text{"}\leq\text{2non-severe"}} + \text{VirLoad}_{\text{"vl50"}} + \text{CD4}_{>500} + \text{HIVtime}_{\text{"0-10"}} + \text{Resistance}_{\text{"none"}} + \text{TherapyClass}_{\text{"PI-stand"}}$$

The following multiple regression models were applied and compared: (i) a linear regression on log transformed data, (ii) GLM with gamma family and log link, and (iii) GLM with inverse Gaussian family and log link function.

Model performance.

The adequacy of the models was assessed using goodness-of-fit measures, quantitative predictive indices, a plot of residuals, and a plot of predicted versus observed costs. The goodness-of-fit was appraised using R^2 for the linear model and McFadden's pseudo-R^2 for each GLM, the value of which was computed as: $R^2 = 1 - \frac{l(\hat{\beta})}{l(\bar{y})}$ where $l(\hat{\beta})$ is the log-likelihood for the fitted GLM and $l(\bar{y})$ is the log-likelihood for the model with just the constant term. The ability to predict was assessed using mean absolute error (MAE), root mean squared error (RMSE),and bias measures:

$$MAE = \frac{1}{n}\sum_k |\hat{y}_k - y_k| \; ; \quad RMSE = \sqrt{\frac{1}{n}\sum_k (y_k - \hat{y}_k)^2} \; ; Bias = \frac{1}{n}\sum_k \hat{y}_k - \frac{1}{n}\sum_k y_k$$

where $\hat{y}_k$ denotes the predicted mean of the total costs for patient k , and y_k denotes the observed values of costs for this patient. The obtained estimates are given in Table 9 (Appendix A).

The quantitative predictive indices were computed on an independent data set. For the further analysis, the model with inverse Gaussian family and the log link function was preferred. Figure 5(Appendix A)illustrates a plot of predicted versus observed costs for this model.

The value of McFadden's pseudo-R^2 suggested that 50% of the total costs could be explained by the selected patient characteristics. The resulting coefficients represent the percentage change in the annual total cost from its average as a response to a one-unit shift in the explanatory variable compared with the reference category. A Wald test was performed to test whether the pairwise difference between the coefficient of the reference class and the other class is different from zero. The *p*-values in Table 4 indicate whether each level's mean is significantly different from the reference level's mean.

***Cost ratios*.**

Application of the log link function was supported by the given distribution of total costs and the model showeda good fit, which made it possible to compute cost ratios between patients with different characteristics using the estimated coefficients. Following the reasoning given by Bloughet al.

(2000)[18], ratios of mean total costs were calculated based on the factors: ARV class, gender, CD4-T cell count, drug resistance, and comorbidity.

We constructed an analytical form of the cost ratio for a patient who differs from the reference patient only in these selected characteristics. Following the notation given in the section on the model specification,these variables have the following number of categorical classes: therapy class: *h*=1,2,3,4,5; CD4-T cell count: l= 1,2,3; comorbidity: *r*=1,2,3 (with levels: ≤2nonsev, >2nonsev, >2severe respectively), gender: *b*=1,2, drug resistance: *j*=1,2 (with levels: "no resistance", "at least three classes"respectively).

As long as the estimated coefficients resulted not on the true scale it is reasonable to analyze the logarithm of the ratio between the total costs for the reference patient and the patient defined above. It is given by:

$$\log(\rho_{bhlrj}) = \log\left(\frac{\mu_{bhlrj}}{\mu_{11111}}\right) = \log(\mu_{bhlrj}) - \log(\mu_{11111})$$
$$= (\mathrm{Gender}_b + \mathrm{TherapyClass}_h + \mathrm{CD4}_l + \mathrm{Comorbidity}_r + \mathrm{Resistance}_j)$$
$$- (\mathrm{Gender}_1 + \mathrm{TherapyClass}_1 + \mathrm{CD4}_1 + \mathrm{Comorbidity}_1 + \mathrm{Resistance}_1)$$

When coding the model, all the reference categories were set to 0. Therefore, using estimated coefficients the costs ratio is simplified to:

$$\hat{\rho}_{bhlrj} = \frac{\hat{\mu}_{bhlrj}}{\hat{\mu}_{11111}} = \exp\left(\hat{\mathrm{Gender}}_b + \hat{\mathrm{TherapyClass}}_h + \hat{\mathrm{CD4}}_l + \hat{\mathrm{Comorbidity}}_r + \hat{\mathrm{Resistance}}_j\right)$$

Confidence intervals for the corresponding cost ratios were also computed using the variance and variance-covariance matrix of the parameter estimates[18]. For example, the following equation illustrates the calculation of variance for the ratio of the mean total costs of male individuals with therapy class "PI-stand", CD4 = ">500", comorbidity = "≤2nonsev" and drug resistance = "no resistance" compared with the mean total costs of male individuals with therapy class "PI-stand",CD4 = "200-500", comorbidity = ">2nonsev" and drug resistance = "three classes":

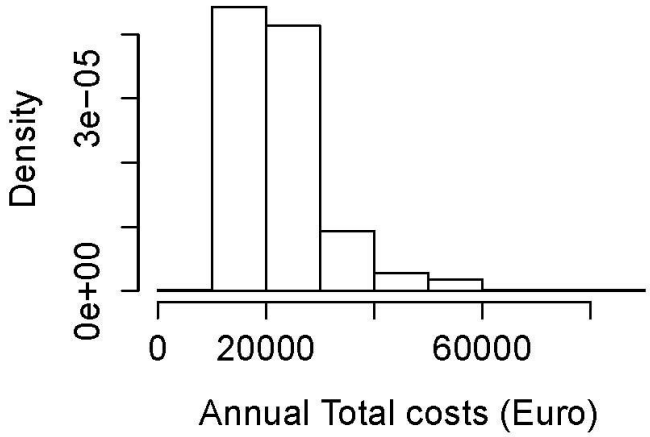
$$Var(\log(\rho_{11222}))$$
$$= Var\left(\widehat{\text{CD4}}_2\right) + Var(\widehat{\text{Comorbidity}}_2) + Var(\widehat{\text{Resistance}}_2)$$
$$+ 2Cov\left(\widehat{\text{CD4}}_2, \widehat{\text{Comorbidity}}_2\right) + 2Cov\left(\widehat{\text{CD4}}_2, \widehat{\text{Resistance}}_2\right)$$
$$+ 2Cov(\widehat{\text{Comorbidity}}_2, \widehat{\text{Resistance}}_2)$$

We obtained the result $Var(\log(\rho_{11222})) = 0.00665326$. Therefore, the 95% confidence interval for $\log(\rho_{11222})$ ranges from 0.20212 to 0.52176 with thecorresponding confidence interval for the true ratio being (1.224,1.685).

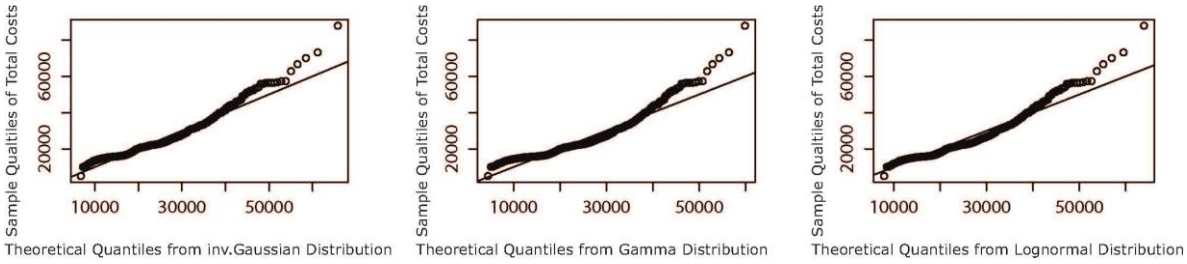
The cost ratios and respective confidence intervals are presented in Table 5 in the main text. The cell with a cost ratio of 1 indicates that all other ratios are estimated relative to these reference categories.

The part of the covariance matrix that is used for the calculations of the cost ratios are given in Table10(Appendix A).

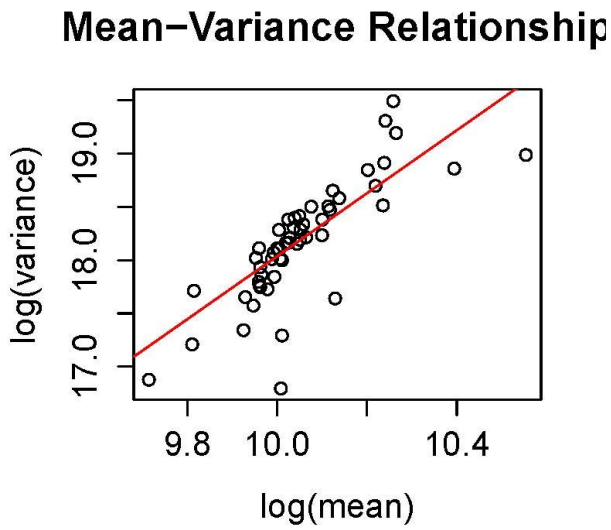
Supplemental Digital Content. Figure 2, Histogram of annual total costs, that relates to the Appendix A and displays distributional characteristics of the annual total costs. This histogram shows skewness of the data to the right.



Supplemental Digital Content. Figure 3, Quintile-quintile (Q-Q) plots of the total costs against theoretical distributions, that relates to the Appendix A and further presents the distributional characteristics of the cost data and shows Q-Q plots of the total costs against three selected theoretical distributions: gamma, inverse Gaussian, and lognormal distributions.



Supplemental Digital Content. Figure 4, Mean-Variance relationship of the annual total costs, that relates to the Appendix A and illustrates mean-variance relationship of the total costs data on the log scale. It supports the choice of inverse Gaussian distribution for the regression analysis.



Supplemental Digital Content. Figure 5, plot observed vs predicted values, that relates to the Appendix A and gives a plot of observed values against predicted values for the model used in the regression analysis (GLM with inverse Gaussian family and the log link function).

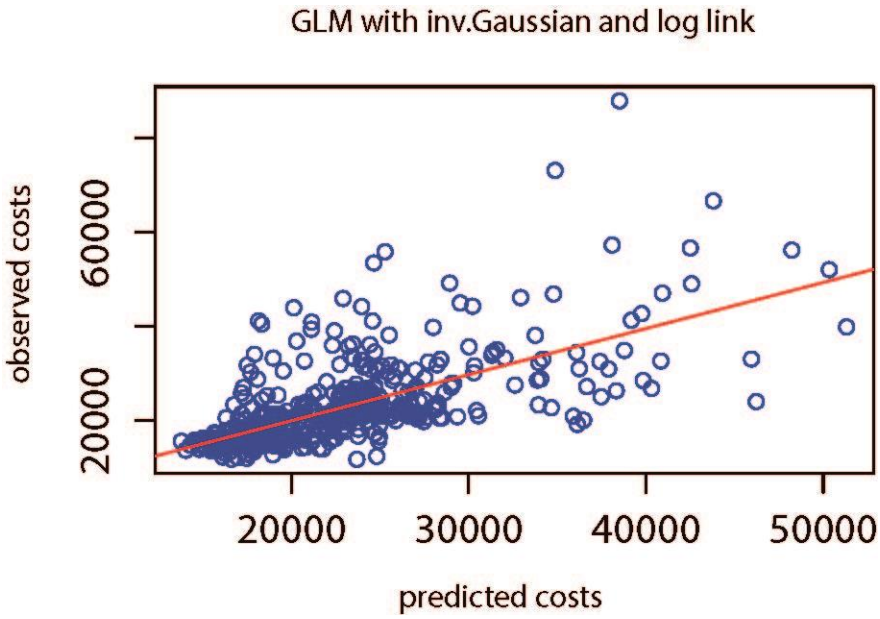


Table 6. Description of the patients' data for the patients who abandoned the survey during the first year of CORSAR (*n*=65).

Variable	**Description**	**Categories**	**Percentage of observations, %**
Age Group	Age group of a patient in years	20-29	10.61
		30-44	36.36
		45-59	42.42
		60+	10.61
		n.a.*	0.00
Gender	Gender	female	7.58
		male	92.42
		n.a.	0.00
Education	The highest educational level achieved	graduated	9.09
		neither nor	59.09
		no school certificate	1.52
		n.a.	30.30
Income	Stable or non-stable income	full-time employment	33.33
		pensioner	18.18
		other	9.09
		n.a.	39.39
HIV related variables			
Time since diagnosis of HIV	Time after initial diagnosis of HIV infection before entering the survey (in years)	0 -10	50.00
		10-20	25.76
		>20	13.64
		n.a.	10.61
CDC class	Class according to the CDC classification system for HIV infection	Category A: Mildly symptomatic	19.70
		Category B: Moderately symptomatic	37.88
		Category C: Severely symptomatic	37.88
		n.a.	4.55
Viral Load	HIV viral load (RNA copies/ml)	<50	66.67
		50-500	10.61
		>500	7.85
		n.a.	15.15
CD4-T	CD4-T cell count (cells/mm^3)	>500	43.94
		200-500	43.94
		<200	10.61
		n.a.	1.52
Treatment related variables			
Therapy Class	Assigned antiretroviral drugs classes	PI-ind	0.00
		PI-standard	1.52
		NNRTI	39.39
		mixed	0.00
		other	59.09
		n.a.	0.00

Therapy Line	Combination antiretroviral therapy (cART) line	first-line	28.79
		second- and third-line	6.06
		beyond the third-line	21.21
		n.a.	43.94
Resistance	Genotypic resistance against antiretroviral medication	no resistance	83.33
		three classes(PI, NNRTI, NRTI) and more	0.00
		NNRTI	3.03
		NRTI	3.03
		NRTI and NNRTI	0.00
		PI	7.58
		PI and NRTI	3.03
		n.a.	0.00
General Health related variables			
Lab ALT	Alanine Aminotransferase Test (U/L)	<110	83.33
		≥110	6.06
		n.a.	10.61
Lab LDL	Low-Density Lipoprotein Cholesterol Test (mg/dL)	<200	65.15
		≥200	0.00
		n.a.	34.85
Lab CREAT	Serum creatinine level test (mg/dL)	< 0.9	42.42
		0.9-1.5	42.42
		>1.5	3.03
		n.a.	12.12
Comorbidity	Number of concomitant diseases and degree the severity of the severest among the diseases.	≤2non-severe	36.36
		≤2 severe	7.58
		>2 non-severe	22.73
		>2 severe	7.58
		none	0.00
		n.a.	25.76
Disability	Disability index according to the German the Disabled Persons Act**	0 – No disability	34.85
		<50 – Intermediate/ Moderate disability	9.09
		≥50 – Severe disability in activities of daily living	30.30
		n.a.	25.76

*not availableobservations

**Grad der Behinderung (GdB), Deutsches Schwerbehindertenrecht

Table 7. Mean of costs (SD) across the eight healthcare provider sitesstratified by cost categories (Euro).

Site	Cost Categories						
	Total*	**cART drugs**	**non-ARV medication**	**Inpatient**	**Outpatient**	**Out-of-pocket**	**Indirect**
1	23124.27 (6632.40)	19094.70 (4544.05)	1107.28 (3789.70)	1769.19 (3448.88)	397.50 (382.53)	310.40 (913.69)	979.56 (1701.80)
2	21402.75 (10648.49)	18517.58 (5232.45)	1264.03 (93776.49)	1260.77 (4909.78)	159.73 (368.58)	223.98 (426.97)	983.34 (1679.37)
3	22574.55 (7415.51)	19089.18 (4328.43)	1874.75 (4707.85)	1094.61 (3269.59)	179.84 (277.04)	123.14 (255.74)	735.38 (2140.92)
4	21653.70 (6975.45)	18057.28 (4872.19)	1263.07 (2789.76)	1039.17 (2854.22)	393.20 (601.07)	381.03 (1115.55)	1349.07 (2743.64)
5	22649.77 (8704.50)	19530.42 (5392.66)	1066.29 (1731.84)	1426.45 (4759.66)	151.62 (213.50)	144.13 (267.04)	876.81 (2404.60)
6	23518.91 (11967.16)	18721.63 (6666.76)	1831.75 (4845.97)	1952.96 (5430.55)	204.64 (318.63)	178.31 (385.81)	5377.92 (10767.95)
7	23053.41 (8886.56)	19586.70 (7154.42)	967.79 (2021.07)	972.73 (2945.61)	294.21 (302.01)	242.24 (433.47)	3175.06 (5776.34)
8	22284.53 (9363.10)	18526.03 (6202.73)	1790.15 (3214.76)	919.52 (2602.03)	244.70 (338.19)	212.93 (470.58)	1560.66 (4155.76)

*The estimates of the annualized total costs presented in Table 7 include also negligible cost fractions e.g. massages, psychological support, nutrition consulting.

Table 8.Data on the annualized costs forpatients who completed both years of the CORSAR survey (n = 942).

Costcategory	**Mean costs (SD)** **(Euro), Data for the first year of CORSAR**	**Mean costs (SD)** **(Euro), Data for the second year of CORSAR**
Total costs	22477.57(8809.45)	22231.03(8786.13)
cART drugs	18852.53(5297.44)	18688.62(5289.48)
non-ARV medication	1499.36(3718.50)	1805.05(5034.45)
Out-of-pocket	212.23(588.61)	200.87(605.36)
Indirect	1462.79(3997.91)	1779.37(4175.84)
Hospital stay	1246.98(3850.15)	984.53(2894.06)
Outpatient costs	237.04(365.61)	240.06(391.10)
Outpatient rehabilitation	81.92(502.85)	63.88(433.77)
Medical gymnastics	55.33(168.31)	56.45(170.99)
Massages	14.34(40.50)	14.66(40.46)
Nutrition support	6.23(39.49)	5.94(35.51)
Inpatientrehabilitation	136.29(704.82)	145.90(804.59)

Table 9. Model performance

Model	Predicted Mean (SD)	R^2or Pseudo-R^2	AIC	MAE	RMSE	Bias
GLM with inverse Gaussiandistribution and log link function	22379.42 (6051.59)	0.5029296	10499	4500.22	6566.329	19.16293
GLM with Gamma distribution and log link function	22360.16 (5984.769)	0.5020352	10575	4076.246	6788.719	-534.6144
OLS, log (naïve)	22215.57 (5169.697)	0.4345	-	4388.54	6895.422	-1246.26

Table 10. Variance-covariance matrix of the parameter estimates (partial).

Coefficients	Gender, male vs. female	CD4, >500 vs. <200	CD4, >500 vs. 200-500	Comorbidity, ≤2nonsev" vs. >2nonsev	Comorbidity, ≤2nonsev vs. >2severe	Therapy Class, PI-stand vs. Mixed	TherapyClass, PI-stand vs. NNRTI	TherapyClass, PI-stand vs. Other	TherapyClass, PI-stand vs. PI-ind	Resistance, no resistance vs. three classes
Gender, male vs. female	1.351104e-03	-5.517828e-05	3.617787e-05	-3.681504e-05	-1.369070e-04	-5.676560e-05	9.074253e-05	7.205964e-05	-1.763722e-05	3.806316e-06
CD4, >500 vs. <200	-5.517828e-05	3.151038e-03	2.865989e-04	1.084944e-04	-1.288990e-04	-1.692336e-04	3.125375e-05	-1.309653e-04	-1.711770e-04	1.481077e-05
CD4, >500 vs. 200-500	3.617787e-05	2.865989e-04	6.392490e-04	5.468792e-05	7.468742e-05	-4.670346e-05	-5.079890e-05	-1.708577e-05	-7.397848e-05	-5.999322e-05
Comorbidity, ≤2nonsev" vs. >2nonsev	-3.681504e-05	1.084944e-04	5.468792e-05	9.992591e-04	4.848478e-04	4.680435e-05	2.297290e-05	-5.675181e-05	8.897262e-05	2.022199e-05
Comorbidity, ≤2nonsev vs. >2severe	-1.369070e-04	-1.288990e-04	7.468742e-05	4.848478e-04	3.914086e-03	1.428715e-04	8.343213e-05	-7.255907e-05	2.348085e-04	-1.401594e-04
Therapy Class, PI-stand vs. Mixed	-5.676560e-05	-1.692336e-04	-4.670346e-05	4.680435e-05	1.428715e-04	2.561858e-03	3.994939e-04	3.834428e-04	3.962514e-04	-1.108174e-04
TherapyClass, PI-stand vs. NNRTI	9.074253e-05	3.125375e-05	-5.079890e-05	2.297290e-05	8.343213e-05	3.994939e-04	9.259000e-04	4.461606e-04	3.705730e-04	1.542004e-04
TherapyClass, PI-stand vs. Other	7.205964e-05	-1.309653e-04	-1.708577e-05	-5.675181e-05	-7.255907e-05	3.834428e-04	4.461606e-04	9.888171e-04	4.040868e-04	1.148104e-04
TherapyClass, PI-stand vs. PI-ind	-1.763722e-05	-1.711770e-04	-7.397848e-05	8.897262e-05	2.348085e-04	3.962514e-04	3.705730e-04	4.040868e-04	5.097338e-03	-8.778012e-04
Resistance, no resistance vs. three classes	3.806316e-06	1.481077e-05	-5.999322e-05	2.022199e-05	-1.401594e-04	-1.108174e-04	1.542004e-04	1.148104e-04	-8.778012e-04	4.985138e-03

Article 5

Estimation of utility values and factors driving health-related quality of life in people living with HIV and AIDS and receiving cART in Germany: analysis of a cohort study

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Estimation of health-state utility values and factors driving health-related quality of life in people living with HIV and AIDS and receiving cART in Germany: analysis of a cohort study.

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Abstract.

Objectives

HIV has become a chronic disease since the widespread of combined antiretroviral therapy (cART). Understanding the influence of therapeutic and preventive interventions on health-related quality of life (HRQoL) of people living with HIV and AIDS (PLWHA) is important. In health economic evaluations the patient benefits are often measured in utilities. Utilities represent the value which the society gives to a specific health state whereas HRQoL takes the perspective of the patients. Commonly required effectiveness measure is quality adjusted life years (QALY) which is calculated using utility values. Information about health state utilities and HRQoL in PLWHA after the introduction of cART is limited, especially in Germany. There are no estimates of HRQoL weights for German PLWHA on cART.

Methods:

This study longitudinally estimated utilities and HRQoL over time in PLWHA in Germany using the generic EQ-5D-3L questionnaire. Health state utilities were calculated based on the EQ-5D descriptive system using the German EQ-5D-3L time trade-off (TTO) value set. HRQoL was calculated based on the EQ visual analogue scale (EQ-VAS). Extensive descriptive analyses were performed to represent utility values for different groups of the patients. Generalized linear models (GLMs) with beta-inflated distributions were used to determine patient characteristics and clinical factors that influence on HRQoL.

Results

1,056 PLWHA completed the EQ-5D-3L questionnaires at the baseline. The mean TTO utility value is 0.912 (SD±0.154) and the mean VAS HRQoL is 84.32 (SD±18.55). Utility and HRQoL decrease with the time living with HIV. The patients with symptomatic HIV infection and AIDS have lower utility values and HRQoL. A higher age, a longer period of living with HIV, a higher CD4-cell count and having symptomatic HIV or AIDS are associated with a lower probability of having HRQoL of perfect health.

Conclusion

Though HIV-infection is a chronic disease, its impact on patients' quality of life is manageable. Provision of additional specific psychological and social support for PLWHA may improve their quality of life.

Keywords: HIV, Quality of Life, Determinants of HRQoL, EQ VAS, TTO, EQ-5D, Germany, PLWHA

Introduction

Combined antiretroviral therapy (cART) sustains HIV-virological suppression and consecutively immunological reconstitution in people living with HIV infection(1, 2). If cART is initiated timely and taken regularly it can prevent HIV transmission, reduce HIV-related morbidity(3) and increase life-expectancy of PLWHA close to that of the general population(4). Nonetheless, HIV infections and HIV-caused morbidity and mortality continue to be a public health issue. In Germany, the Robert Koch institute estimated 86,000 (80,000 – 92,400) people living with HIV with 68,800 receiving cART by the end of 2017 (5).

Given the current public health burden of chronic HIV infections and ongoing research and development of new therapies(3), prevention strategies(6) and screening programs, health economic evaluations are required to provide information for decision-making in HIV-management. Economic evaluations comprise of weighing the costs and benefits of alternative strategies and provide comparative analyses of payoffs of different courses of action (7). Quality adjusted life years (QALYs) is a widely applied measure of health outcomes in economic evaluations and recommended by the Second Panel on Cost-Effectiveness in Health and Medicine(8) as well as by several decision-making bodies in public health, including: National Institute for Health and Clinical Excellence (NICE)(9), Canadian Agency for Drugs and Technologies in Health (CADTH)(10), Pharmaceutical Benefits Advisory Committee (Australia)(11), the National Health Care Institute in the Netherlands(12) and the Standing Vaccination Committee (STIKO)(13) at the German Robert-Koch Institute. Additionally, due to the chronic nature of HIV infection measurement of health-related quality of life plays a crucial role in our understanding of the impacts of life-long therapeutic interventions on the patients' health. Furthermore, analyses of the data allow identification of the most influential factors which can be addressed when aiming to improve HRQoL.

In order to calculate QALY for a given health condition health utilities (also known as quality of life weights) are necessary. For application in health economic evaluations indirect elicitation methods, which are based on pre-scored generic preference-based measures, are preferred (14). EuroQol (EQ)-5D(15), the Short Form 6D (SF-6D)(16) and the Health Utilities Index (HUI)(17) constitute commonly used generic questionnaires applied in measurement of health utility values.

In this study we evaluate health utilities in a German multicenter cohort of PLWHA who receive cART using the EuroQol instrument. The study is based on the data collected in a nationwide multi-centre, non-interventional, prospective 96-week survey conducted in PLWHA in Germany: "Cost and Resource Utilisation Study in Antiretroviral Therapy (CORSAR)". The survey has been previously described in a paper by Kuhlmann et al. who provide a summarization of the collected data for the 48-week period and report the costs and utility

values across three therapy lines(18). Another study thoroughly examines and describes the cost data of CORSAR(19). The present study reports the HRQoL data collected over the whole period of the survey in greater detail and identifies influential clinical and therapy-related factors.

Methods

Study population

Inclusion criteria for CORSAR were: (i) HIV positive diagnosis, (ii) age of at least 18 years, and (iii) receiving cART at the study entry. The survey was not intended to include primarily treatment, i.e. naïve patients. The observation period was 96 weeks between April 2009 (first patient started) and April 2012 (last patient finished) with scheduled quarterly visits at the involved physicians. The participating physicians from the four hospitals and eight private practices specialized in HIV went through a six-month preparation period with baseline examinations. The CORSAR study population included 1,154 PLWHA representing a 2.3% sample of treated PLWHA in Germany.

The data were collected using the self-reported questionnaires and from the clinical records of the participants, and include: demographical characteristics (age, gender, education, employment), HIV- and general health-related records (CD4-T cell count, viral load, disability, comorbidities, conditions, results of laboratory tests), details of diagnosis (time after initial diagnosis of HIV infection, CDC category) and records of the antiretroviral therapy (line of antiretroviral regimen at start of the study, medications, genotypic resistance tests).

Measurement of quality of life

In CORSAR, the preference-based EQ-5D-3L self-reported questionnaire was employed for measurement of HRQoL. EQ-5D contains the descriptive system and the visual analogue scale. The EQ-5D-3L descriptive system comprises of five domains (mobility, self-care, usual activities, pain/physical discomfort, anxiety/ depression). Each domain was assessed by the patients using in three levels of perceived problems (none, moderate, severe). Different combinations of the recorded levels for the five areas were weighted based on the preferences identified by the general population for which the tariffs from Germany were used. This weighted utility summary score is further referred to as (TTO) utility value.

The EQ-VAS is a scale reaching from 0-100 (worst imaginable health state – best imaginable health state) on which patients mark how good or bad they assess their current health. This scale is another measure of HRQoL. In CORSAR, the participants were asked to fill out the questionnaires at all visits. For the following analyses only those participants were include who completed the EQ-5D-3L questionnaire.

Ethical review

The CORSAR survey was approved by the national regulatory authorities and local ethics committees of all participating centres. All patients were given thorough information on the survey. Before the participation in the interviews, the patients provided written consent. No incentive was offered to the patients for their participation in the survey.

Data analyses

Descriptive and regression analyses were carried out. The regression analysis was performed to identify factors which were associated with HRQoL in PLWHA. A generalized linear model was fitted using a three-parameter beta-inflated distribution for the TTO utility values and a four-parameter beta-inflated distribution for the VAS HRQoL values. This distribution type is able to account for the nature of the quality of life measures being bound between the values zero and 1. The selection of the predictor variables was based on expert opinion and a systematic review of relevant factors on quality of life of HIV patients(20). All metric variables were transformed to z-scores by subtracting their mean and dividing by their standard deviation. Levels of the categorical variables were clustered via the fusion-based approach (21). A random intercept was included to capture the hierarchical structure of the data. All analyses were carried out using R software (version 3.4) and the *gamlss* package. The function *pcat()* was used for the level reduction of categorical variables with the method GAIC and LP1 (lasso-type) penalty and the *random()* function for the random intercept.

Results

Study population

Out of the recruited 1,154 patients, 1,056 completed the EQ-5D-3L questionnaires at the first visit (further baseline). Table 1 presents the socio-demographic and the clinical characteristics of the participants who completed the questionnaires at baseline (all visits are given in supplemental tables: S1 and S2). The sample encloses mostly male HIV-infected patients (88.8%) and those in the 30-60 age group (82.7%). Majority of the participants have school-level education (70.7%) and have a steady income: employed (39.6%) and retired (22.8%). At baseline, 42% of the participants were listed in category CDC-B (symptomatic HIV infection), 28.6% were in category CDC-A (asymptomatic HIV infection) and 27.1% were in category CDC-C (AIDS-indicator). Majority of the participants had CD4 counts over 200cells/µL (93.5%) and HIV viral load below quantification limit (less than 50 copies/mL, 89.9%) at baseline. 82.6% of the participants had comorbidities. Of them, 58 patients had lipodystrophy, 13 - diabetes mellitus, 35 - Hepatitis C, 52 - Hepatitis B, and 8 participants had depression (see S1 in supplement). Other comorbidities were categorized into groups which are presented in Table 1. The table also gives the clinical characteristics of the patients for other visits.

Table 1: Socio-demographic and clinical characteristics of the patients in CORSAR. (n=participants who completed EQ-5D-3L questionnaires at baseline)

Socio-demographic Characteristics	at Visit 0 (Baseline) (n=1056)		Clinical Characteristics	at Visit 0 (Baseline) (n=1056)	
Age (mean. SD)	47.6	11.0	Years since diagnosis of HIV (mean. SD)	10.7	7.0
Age (n.%)			HIV infection stage (CDC classification) (n. %)		
<20 years old	1	0.1	Asymptomatic (Category A)	302	28.6
20-29 years old	43	4.1	Symptomatic (Category B)	443	42
30-39 years old	207	19.6	AIDS-Indicator (Category C)	286	27.1
40-49 years old	444	42	Not recorded	25	2.4
50-59 years old	223	21.1	CD4+ cell count (n. %)		
>60 years old	138	13.1	<200 cells/µL	65	6.2
Gender (n.%)			200-499 cells/µL	402	38.1
Male	938	88.8	≥500 cells/µL	585	55.4
Female	112	10.6	Not recorded	4	0.4
Transsexual	6	0.6	HIV viral load (different grouping) (n. %)		
Education level (n.%)			Below quantification limit	949	89.9
No qualifications	88	8.3	<10.000	90	8.5
Secondary school leaving certificate (leaving after 9th grade)	243	23	10.000-100.000	7	0.7
Intermediate school-leaving certificate (leaving after 9th grade)	308	29.2	≥100.000	6	0.6
School diploma corresponding to university entrance level	195	18.5	Not recorded	4	0.4
Professional training	86	8.1	Comorbidity (n. %)		
University	115	10.9	Presence of comorbidity	872	82.6
Other	3	0.3	1-4 conditions	655	62
No response	88	8.3	>5conditions	216	20.5
Employment status (n. %)			Allergy	188	17.8
Full-time employed	418	39.6	Dermatological	286	27.1
Part-time employed	77	7.3	Respirational	183	17.3
Self-employed	73	6.9	Cardiovascular	248	23.5
Unemployed	95	9	Endocrine	134	12.7
Retired	241	22.8	Gastro-intestinal	249	23.6
House	17	1.6	Haematological	89	8.4
In study	10	0.9	Neurological	145	13.7
Other	17	1.6	Psychiatric	209	19.8
No response	108	10.2	Other	601	56.9

Classes of antiretroviral regimens were categorized into three groups, according to the treatment status of the patient and in accordance with the existing German treatment guidelines: “standardized” and “individualized”. “Standardized” regimens included either NNRTI (non-nucleoside reverse transcriptase inhibitor)-based regimen, consisting of one NNRTI in addition to nucleos(t)ide analogues or PI (Protease inhibitor)-based regimen, consisting of one ritonavir-boosted PI (PI/r) in addition to nucleos(t)ide (NRTI) analogues, which summarizes regimens of cART recommended as preferred in the actual German-Austrian treatment guidelines at the time of the study conduction(22). “PI-individualized” class was assigned to the PI/r-based cART regimens in patients with a history of multiple treatment failure and acquiring multi-resistant HIV. Their regimens consist of the elements of more than two different antiretroviral classes and more than three different antiretroviral substances including boosted PIs, “other cART regimens” are those that did not meet the criteria of the standardized and individualized PI/r-based regimens. The cART regimens used in the survey are summarized in Table S3 in the supplement. At the start of CORSAR-study the first integrase strand transfer inhibitors (INSTI) was newly available in Germany. Hence, at baseline, most of the patients received PI-based regimens (516 patients) and NNRTI-based regimens (292 patients).

Estimation of utility values and HRQoL values

Table 2 summarizes most reported health states at baseline, the recorded levels for the five EQ-5D areas and mean and standard deviations for TTO utility scores and HRQoL VAS scores (see Table S4 for all visits in the supplement). For the total sample, the mean TTO score is 0.912 (±0.154) with 59.3% ranging from 0.9 to 1.0 and the mean VAS score is 84.32 (±18.55) with 54.5% ranging from 90 to 100. For the five EQ-5D domains, most patients report “no problems” in the “mobility” (83.8%) and “self-care” (97.7%). In contrast, in the areas “emotional health” and “physical discomfort” a large part of the patients reports “some problems” (24% and 32% respectively).

Table 2: Records of measurement of quality of life of the patients in CORSAR at baseline (n=1056)

Most reported health states at baseline (n.*% of total*)			EQ-5D-3L domains and levels (n.%)			
11111	479	45.4	Mobility	None	885	83.8
11112	111	10.5		Some	171	16.2
11121	96	9.1		Severe	0	0
11122	96	9.1	Self-care	None	1032	97.7
11212	13	1.2		Some	23	2.2
11221	16	1.5		Severe	1	0.1
11222	46	4.4	Usual activities	None	857	81.2
21121	26	2.5		Some	187	17.7
21122	21	2		Severe	12	1.1
21221	20	1.9	Pain/discomfort	None	632	59.8
21222	36	3.4		Some	395	37.4
TTO value mean, SD	0.912	0.154		Severe	29	2.7
			Anxiety/depression	None	664	62.9
VAS value mean. SD	84.32	18.55		Some	366	34.7
				Severe	26	2.5

Additionally, Table 3 presents the mean estimates of TTO utility values by CDC category, age group, group of years since HIV diagnosis and cART regimen (at baseline).

Mean estimate of TTO utility values at baseline for the patients who have AIDS (listed in CDC class C) lower than for people who have no AIDS. The descriptive analysis of utility values across age groups does not allow the conclusion that health state utilities decrease in older people. The variation for CDC category A is between 0.927 (40-49 year olds (yo)) and 1.00(<20 yo) and for CDC B is 0.963 (20-29yo) – 0.889 (50-59yo). For CDC category C the older people seem to have worse utility vales with a range of 0.934 (20-29 yo) – 0.855 (>60yo).

Table 3: TTO utility values (mean, SD) across CDC categories and by age group, years living with HIV and cART regimen at baseline (n=1056)

CDC category	TTO utility values (mean, SD)					
	Age groups					
	<20	20-29	30-39	40-49	50-59	>60
CDC-A	1.000, na	0.980, 0.044	0.951, 0.101	0.927, 0.129	0.941, 0.108	0.946, 0.136
CDC-B	na	0.963, 0.070	0.935, 0.140	0.901, 0.167	0.889, 0,173	0.919, 091
CDC-C	na	0.934, 0.076	0.928, 0.157	0.892, 0.178	0.857, 0.181	0.855, 0.244
CDC category	***Years living with HIV***					
	<10		10 -20		>20	
CDC-A	0.960, 0.081		0.928, 0.151		0.846, 0.146	
CDC-B	0.911, 0.167		0.922, 0.112		0.882, 0.145	
CDC-C	0.914, 0.179		0.882, 0.154		0.818, 0.241	
CDC category	***cART regimen***					
	NNRTI individ.	NNRTI standard.	PI individ.	PI standard.	Other	Therapy <14 days
CDC-A	0.943, 0.065	0.946, 0.133	0.931, 0.073	0.922, 0.131	0.962, 0.081	0.962, 0.065
CDC-B	0.866, 0.101	0.902, 0.162	0.871, 0.210	0.913, 0.150	0.928, 0.121	na
CDC-C	0.662, 0.287	0.874, 0.204	0.829, 0.230	0.896, 0.148	0.942, 0.141	0.944, 0.080

The consideration of cART regimen suggests higher utility values for PI-based regimen than for NNRTI-based regimen in the patients listed in CDC categories B and C. Analysis of mean estimates of TTO utility values by the “years since HIV” groups suggests worsening of quality of life with time. Figure 1 illustrates TTO utility values plotted against years since HIV-diagnosis for the whole sample.

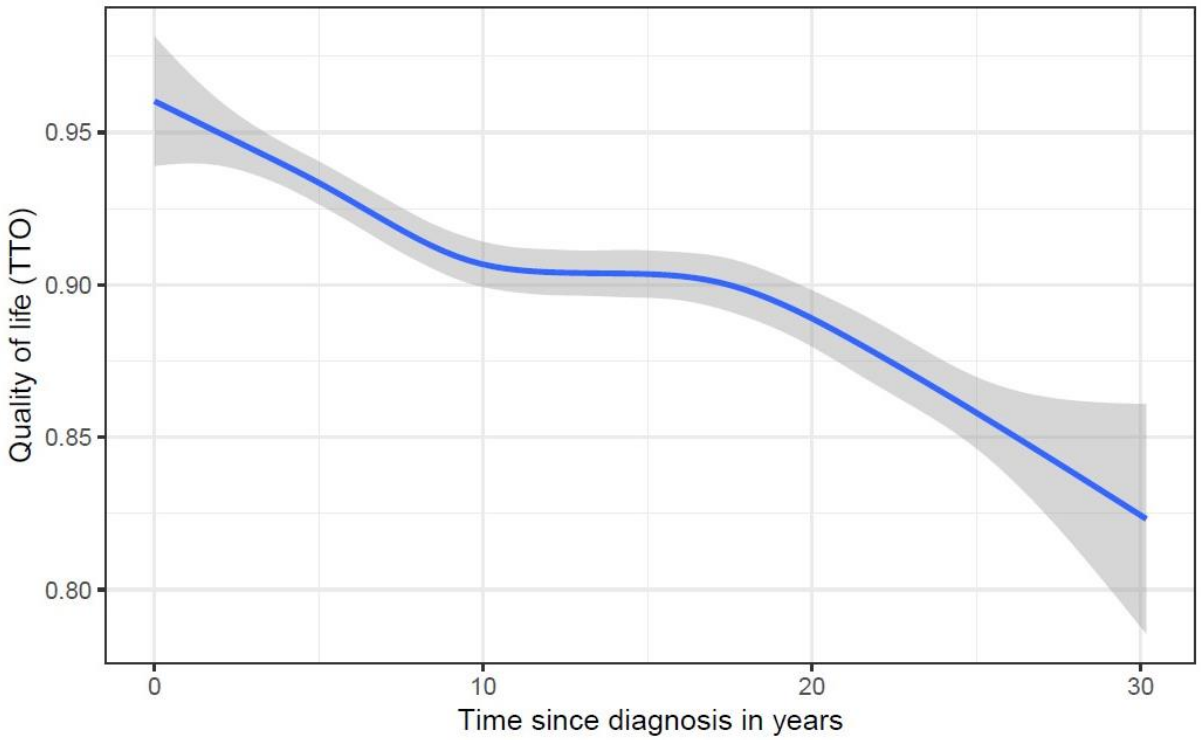

Figure 1. TTO utility values in dependence on time living with HIV (years).

Descriptive analysis does not allow identification of impact of each factor on the utility values. The following section describes the results of the regression analysis conducted to determine the effects of separate patient characteristics on the utility values.

Driving factors

The results of the explanatory models of health state utilities and HRQoL can be seen in Table 4. The main focus will be on the utility scores, as these are more relevant to health economic evaluations. Clustering the factor levels of the variables “Education”, “Job” and “Treatment” in the utility model lead to a reduction in factor levels from 7 to 4, 7 to 3 and 7 to 5, respectively. For education, patients with no or other education and secondary school (grade 9) were summarized into one category and high school and university were clustered together. Middle school (grade 10) and patients with a vocational training remained in a single level, respectively. In the VAS model, patients with high school and university degree showed a similar effect as patients in the category “none/other/secondary school” and were grouped into one level.

Table 4: Results of the GLM model of the analysis of TTO values and VAS scores via a beta-inflated distribution.

	TTO	VAS
Mu (logit-link)		
mu Intercept	1.950 (0.065)***	1.095 (0.054)***
Age in years (z-score)	-0.114 (0.019)***	-0.085 (0.008)***
Gender: male	Reference	Reference
Gender: transsexual	0.213 (0.180)	-0.060 (0.114)
Gender: female	0.223 (0.052)***	-0.115 (0.028)***
Education: vocational training	Reference	Reference
Education: junior high school	0.355 (0.052)***	0.136 (0.025)***
Education: none/other/secondary school	0.480 (0.052)***	-
Education: high school/university	0.276 (0.054)***	-
Education: none/other/secondary school/high school/university		0.188 (0.023)***
Job: Retired	Reference	-
Job: House/student	-	Reference
Job: Part-time	-0.153 (0.054)**	0.524 (0.052)***
Job: Full-time/house/other/self-employed/student/unemployed	-0.104 (0.034)**	-
Job: Unemployed	-	0.147 (0.053)**
Job: Other/retired	-	0.376 (0.049)***
Job: Self employed	-	0.257 (0.054)***
Job: Full-time	-	0.258 (0.048)***
No. of co-morbidities (z-score)	0.020 (0.016)	-0.055 (0.008)***
Lipodystrophy	0.092 (0.059)	0.092 (0.030)**
Diabetes	0.530 (0.136)***	0.147 (0.055)**
Hepatitis C	-0.920 (0.084)***	-0.595 (0.042)***
Hepatitis B	0.012 (0.070)	-0.316 (0.036)***
Depression	-0.192 (0.257)	-0.439 (0.137)**
Years with HIV (z-score)	-0.028 (0.003)***	-0.023 (0.001)***
CDC Group A	Reference	Reference
CDC Group B	-0.088 (0.041)*	-0.139 (0.017)***
CDC Group C	-0.249 (0.045)***	-0.031 (0.020)
CD4 cell count (z-score)	0.087 (0.016)***	0.092 (0.008)***
Viral load < quantification limit	Reference	Reference
Viral load <10,000	-0.015 (0.060)	-0.024 (0.030)
Viral load 10,000 - 100,000	-0.037 (0.172)	-0.078 (0.090)
Viral load >100,000	-0.829 (0.230)***	-0.225 (0.127)
No. of treatment changes (z-score)	-0.023 (0.013)	-0.065 (0.006)***
Tx: PI norm	Reference	-
Tx: NNRTI norm	-	Reference
Tx: NNRTI ind/NNRTI norm/break	0.012 (0.037)	-
Tx: therapy < 14 days	0.518 (0.266)	-
Tx: PI ind	0.185 (0.049)***	-
Tx: Sonst	0.235 (0.042)***	0.307 (0.020)***
Tx: NNRTI ind/PAUSE/PI ind/PI norm/therapy < 14 days	-	0.057 (0.017)***
Sigma (logit-link)		
sigma Intercept	-0.826 (0.042)***	-1.457 (0.023)***
Age in years (z-score)	-0.007 (0.019)	-0.067 (0.012)***
Gender: transsexual	-0.579 (0.250)*	0.120 (0.183)
Gender: female	-0.251 (0.055)***	0.278 (0.040)***
Years with HIV (z-score)	-0.006 (0.003)*	0.004 (0.002)*

CD4 cell count (z-score)	0.093 (0.016)***	0.074 (0.011)***
CDC Group A	Reference	Reference
CDC Group B	0.160 (0.042)***	0.000 (0.001)
CDC Group C	0.205 (0.046)***	0.018 (0.026)
Nu (log-link)		
nu Intercept		-6.674 (0.784)***
Age in years (z-score) (3)		0.042
Gender: transsexual (3)		-13.490 (49.375)
Gender: female (3)		-15.412 (56.410)
Years with HIV (z-score) (3)		0.079 (0.032)*
CD4 cell count (z-score) (3)		-0.229 (0.733)
CDC Group B (3)		-18.015 (78.485)
CDC Group C (3)		-18.266 (72.719)
Tau (log-link)		
tau Intercept	0.455 (0.066)***	-3.117 (0.165)***
Age in years (z-score) (4)	-0.114 (0.030)***	-0.127 (0.074)
Gender: transsexual (4)	-0.251 (0.474)	-15.670 (58.885)
Gender: female (4)	0.154 (0.092)	0.935 (0.178)***
Years with HIV (z-score) (4)	-0.047 (0.005)***	-0.026 (0.011)*
CD4 cell count (z-score) (4)	-0.066 (0.030)*	-0.222 (0.078)**
CDC Group B (4)	-0.234 (0.068)***	-0.181 (0.178)
CDC Group C (4)	-0.236 (0.075)**	0.418 (0.175)*
Num. obs.	5179	5179
Nagelkerke R^2	0.446	0.727
Generalized AIC	433.094	-8410.667

***p < 0.001, **p < 0.01, *p < 0.05

For the variable “Job”, all levels besides “retired” and “part-time” were grouped into one level for the TTO utility score model, but in the VAS HRQoL model only “other” and “retired” as well as “house” and “study”, respectively, were grouped into one level. For the different treatments, the levels “PI-stand”, “PI-ind”, “therapy < 14 days” and “other” remained as individual levels in the utility model while “NNRTI-ind”, “NNRTI-stand” and “break” were grouped together. In the HRQoL model, “NNRTI-stand” and “other” remained as individual levels and all other treatment options showed similar effects on the HRQoL and were thus summarized into one level.

Regarding the mu parameter of the beta distribution (corresponding to the mean) the intercept of 1.950 corresponds to an utility value of 0.875 given all metric variables being at their mean and for male patients with vocational training, being retired, in CDC category A, a viral load below the quantification limit and PI-standardized treatment.

All the coefficients should be interpreted in relation to this reference case. Starting with the socio-demographic variables, each increase of the age by one standard deviation decreases the estimate of utility value. For example, the patients who are 1 standard deviation (SD) (10.2 years) older than the mean age of 47.4 years have utility value of 0.862. No significant difference in the estimates was found for transgender patients, but women show a significantly higher utility value of 0.898. Compared to persons with a vocational training as the highest level of education, patients with high school diploma or a university degree have a higher utility

value (0.903). Patients with middle school or no or the lowest school degree have even higher utility value estimates with 0.909 and 0.919, respectively. In the context of occupational levels, part-time employed persons show a decreased utility value of 0.858 compared to retired patients. This is also true for persons falling into the last category of full-time workers, students and unemployed although to a lesser extent (0.864).

The quality of life is further altered by the comorbidities of the patients. In the utility model however, the number of comorbidities as well as lipodystrophy, hepatitis B and depression show no significant association with utility values. Patients with diabetes seem to even have a higher utility value of 0.923. On the other hand, patients with hepatitis C have a lower utility value of 0.737.

With respect to HIV-related variables, utility values are also negatively associated with a longer time of living with HIV. Increasing this time by 6.8 years above the mean of 10.4 years corresponds to a lower utility value of 0.872. The disease stage classified into the CDC categories is also associated with the utility values: compared to category A, the patients listed in the category B have a significantly utility value of 0.866 and the patients in the category C (AIDS) show an even lower utility value of 0.846. In addition, the coefficient of 0.087 for the CD4 cell count corresponds to utility score of 0.885 when increasing the mean CD4 cell count of 605 by 281 (i.e. 1 SD). The utility model suggests no significant differences between the viral load between the levels “below quantification limit”, “<10,000” and “10,000 – 100,000”. A viral load above 100,000 is associated with a strong and significant decrease in utility value (0.754).

The last group of variables captures the cART-related factors. The number of changes in the treatment regime seems to show no significant association with the quality of life weights, although the p-value of 0.07 is slightly above the threshold of 0.05. The coefficient would suggest, that utility value is lower with an above average number of treatment changes. Compared to the reference level “PI-stand”, the patients with the summarized level “NNRTI-stand/NNRTI-ind/break” show no significant difference in their HRQoL weights. If the therapy started just within 14 days of data collection, the utility value is higher (0.922) but this association is not significant at the 0.05 level (p-value 0.051). Being treated with “PI-ind” or “other” is associated with a significantly higher utility values of 0.894 and 0.899, respectively.

Discussion

This study is an analysis of quality of life data collected in a major longitudinal study undertaken between 2009 and 2012 in people living with HIV and AIDS in Germany. This multi-centric, nationwide study draws on a large sample by including the main healthcare providers for PLWHA and provides a representative population to study HRQoL.

The results suggest that the mean EQ-VAS value obtained in this study (84.3) is comparable with EQ-VAS estimated for the general population in 2009 (79.2)(23), although based on the reported characteristics of the sample representing the general population it is difficult to explain why the self-reported quality of life in the patients of CORSAR is higher than that of the general population.

This study shows the dimensions of quality of life that are the most affected are “anxiety/depression” and “pain/physical discomfort”, while “mobility” and “self-care” are minor problems. This supports the preliminary results from Investigation on Antiretroviral Therapy (IANUA) and highlights the need to improve specific psychological and social support for PLWHA(24).

In order to distinguish effects of different patient characteristics we conducted a regression analysis using a GLM with beta-inflated distributions. The estimation of the coefficients of sigma parameter indicates which variables are associated with the variance of health utilities in HIV patients. The estimated coefficients suggest that the variance is not associated with age, but that the variance is smaller for transsexual and female patients, i.e. male patients show a greater variance in their utility values than those two groups. Living with HIV for a longer time also seems to be associated with a lower variance. On the contrary, having a CD4 cell count above the mean seems to lead to a higher variance of utility values of the patients and the patients with symptomatic HIV infection (CDC-B) and AIDS (CDC-C) also seem to be more different with regard to the utility values than the patients with asymptomatic HIV infection (CDC-A).The nu-parameter was only estimated for the VAS model, as there were no zero values obtained using the TTO method. This parameter reflects the probability of having a HRQoL score of zero. The only factor that is significantly associated with this probability is the time living with HIV. A longer period of time with HIV is thereby associated with a significantly higher probability of VAS score of zero. The probability of having utility value of 1 (i.e. being in perfect health) is estimated via the tau-parameter. For the utility model, a higher age, a longer period of living with HIV, a higher CD4-cell count and having symptomatic HIV (CDC B) or AIDS (CDC C) are associated with a lower probability of being in perfect health. The gender of patients seems to have no significant effect on having utility value of 1.

Investigation of HRQoL can help us to provide means for its improvement, necessitating examination of influential factors. This research can contribute to the development of better HIV management programs. Our findings confirm previous research which found that time since diagnosis and disease stage to be negatively related to HRQoL, even in those treated anti-retrovirally for a longer duration with the recently available options of cART(25–27). Hence, our study support the recent development of treatment guidelines, which recommend the initiation of cART even in asymptomatic patients with normal CD4-T cell counts (28), because it appears that HRQoL will remain impaired for a longer period in those with more

progressed stages of disease or immunodeficiency. This concept is intuitive due to untreated HIV infection which progresses to a further stage will diminish physical health. Indeed, the poorest physical health is observed in people whose HIV has progressed to AIDS(29). However, in contrast to our study, Jia et al showed that while a higher CD4-T cell count was associated with worse HRQoL at baseline, the same CD4-T cell counts were predictive of higher HRQoL scores 12 months later(30). Though this finding may be counter-intuitive, it is possible that the initial psychological impact of a high CD4-T cell count is significant but that over time, PLWHA more readily accept a high CD4-T cell count by several coping strategies and hence are less likely to experience changes in HRQoL based on this specific factor. Our regression analysis showed a statistically significant negative impact of time living with on the quality of life, which may support the previously stated assumption that people who live with HIV over long time periods experience accumulated negative effects in HRQoL(25, 26).

This study did not reveal a differential impact of the use standardized antiretroviral regimen but lower impairment of HRQoL in the patients receiving PI-individualized regimen, supporting the national guidelines of the German AIDS Association(Deutsche AIDS Gesellschaft, DAIG)(22), which allows physicians to choose between a broad spectrum of available options of cART. The German policy is distinct from most foreign guidelines, giving physicians the opportunity to personalize the treatment, adapting cART regimens based on individual patients' reactions. An administrative database analysis of approximately four million beneficiaries showed that German physicians use this flexibility and are more likely to prescribe patients who are in a more advanced disease state (CDC class C) with a PI/r based regimen than with a NNRTI based regimen(31). The same result was obtained in another observational study in Germany(32).

Limitations

This study has several limitations that need to be addressed. This observational study did not pre-define endpoints and is not statistically powered for more extensive subgroup-analyses. Further, we utilized the EQ-5D questionnaire, which is a "non-disease-specific instrument". Although it allowed estimating quality of life weights applicable for economic evaluations, it may be relatively insensitive tool for measuring the specific HRQoL in PLWHA. Future studies should test the robustness of our results with alternative instruments such as HIV-specific questionnaires like the WHOQOL-HIV Instrument(33). Finally, the study period occurred before the integrase strand transfer inhibitors (INSTI) elvitegravir and dolutegravir became available, which are meanwhile widely used as components of cART in Germany.

Conclusions

As long as HRQoL in PLWHA shows wide variations across the socio-demographic and the clinical characteristic of individuals, measuring HRQoL and determining factors affecting

HRQoL can help to understand to what extent HRQoL is affected by the infection and cART treatment. This analysis used the EQ-5D-3L measurement of utility values (quality of life weights) and determined the factors which influence on HRQoL. The results of this study can inform development and evaluation of HIV-related intervention strategies to improve health-related quality of life in people living with HIV and AIDS in Germany.

List of abbreviations

AIDS	acquired immune deficiency syndrome
ARV	Antiretroviral
cART	combination antiretroviral therapy
CDC	Centers for Disease Control and Prevention classification system
CORSAR	Cost and Resource Utilization Study in Antiretroviral Therapy
EQ-5D	EuroQol five dimensions questionnaire
EQ-5D-3L	EuroQol five dimensions questionnaire three-level scale
GLM	generalized linear model
HIV	the human immunodeficiency virus
HRQoL	health-related quality of life
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PLWHA	people living with HIV and AIDS
QALY	quality-adjusted life year

Declarations

Ethics approval and consent to participate

The CORSAR survey was approved by the national regulatory authorities and local ethics committees of all participating centres. All patients were given thorough information on the survey. Before the participation in the interviews, the patients provided written consent. No incentive was offered to the probands for their participation in the survey.

Consent for publication

Not applicable

Availability of data and material

Please contact author for data requests

Competing interests

By the fact that the patients had been receiving cART before the enrollment into the study, the selection of cART regimen in the sample was not influenced by the authors.

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Literature Cited

1. Pichenot M, Deuffic-Burban S, Cuzin L, Yazdanpanah Y. Efficacy of new antiretroviral drugs in treatment-experienced HIV-infected patients: a systematic review and meta-analysis of recent randomized controlled trials. HIV Med 2012; 13(3):148–55.

2. Teeraananchai S, Kerr SJ, Amin J, Ruxrungtham K, Law MG. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV Med 2017; 18(4):256–66.

3. Cihlar T, Fordyce M. Current status and prospects of HIV treatment. Curr Opin Virol 2016; 18:50–6.

4. Gueler A, Moser A, Calmy A, Günthard HF, Bernasconi E, Furrer H et al. Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. AIDS 2017; 31(3):427–36.

5. Robert Koch-Institut. Schätzung der Zahl der HIV-Neuinfektionen und der Gesamtzahl von Menschen mit HIV in Deutschland. Stand Ende 2017: [Estimation of the number of new HIV infections and the total number of people with HIV in Germany as of the end of 2017]. Epidemiologisches Bulletin 2018 [cited 2019 Sep 2]; (47):509–22. Available from: URL: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2018/Ausgab.

6. Heneine W, Kashuba A. HIV prevention by oral preexposure prophylaxis. Cold Spring Harb Perspect Med 2012; 2(3):a007419.

7. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2011. (Handbooks in health economic evaluation series). Available from: URL: http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=1689059.

8. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016; 316(10):1093–103.

9. NICE. Developing NICE guidelines: the manual: Process and methods; 2014 [cited 2019 Aug 23]. Available from: URL: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview.

10. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada; 2017 [cited 2019 Aug 23]. Available from: URL: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

11. Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee; 2016 [cited 2019 Aug 23]. Available from: URL: https://pbac.pbs.gov.au/.

12. Zorginstituut Nederland. Guideline for economic evaluations in healthcare; 2016 [cited 2019 Aug 23]. Available from: URL: https://tools.ispor.org/PEguidelines/source/Netherlands_Guideline_for_economic_evaluations_in_healthcare.pdf.

13. STIKO. Methoden zur Durchführung und Berücksichtigung von Modellierungen zur Vorhersage epidemiologischer und gesundheitsökonomischer Effekte von Impfungen für die Ständige Impfkommission [cited 2018 Aug 23]. Available from: URL: https://www.rki.de/DE/Content/Kommissionen/STIKO/Aufgaben_Methoden/Methoden_Modellierung.pdf?__blob=publicationFile.

14. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull 2010; 96:5–21.

15. Kind P. The EuroQol Instrument: An Index of Health-Related Quality of Life. uality of Life and Pharmacoeconomics in Clinical Trials 1996; (2):191–201.

16. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002; 21(2):271–92.

17. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. Health Qual Life Outcomes 2003; 1:54.

18. Kuhlmann A, Mittendorf T, Hower M, Heiken H, Gerschmann S, Klauke S et al. Krankheitskosten von HIV-Patienten unter antiretroviraler Therapie in Deutschland - Ergebnisse einer 48-Wochen-Interimsanalyse im Rahmen der prospektiven multizentrischen Kohortenstudie "CORSAR". Gesundheitswesen 2015; 77(6):e133-42.

19. Treskova M, Kuhlmann A, Bogner J, Hower M, Heiken H, Stellbrink H-J et al. Analysis of contemporary HIV/AIDS health care costs in Germany: Driving factors and distribution across antiretroviral therapy lines. Medicine (Baltimore) 2016; 95(26):e3961.

20. Degroote S, Vogelaers D, Vandijck DM. What determines health-related quality of life among people living with HIV: an updated review of the literature. Arch Public Health 2014; 72(1):40.

21. Tutz G, Gertheiss J. Regularized regression for categorical data. Statistical Modelling 2016; 16(3):161–200.

22. Deutsche AIDS-Gesellschaft. Deutsche AIDS Gesellschaft und Österreichische AIDS Gesellschaft Deutsch-Österreichische Leitlinien zur antiretroviralen Therapie der HIV-Infektion: Stand März 2012, AWMF-Register-Nr. 055/0001; 2012 [cited 2012]. Available from: URL: http://www.daignet.de/site-content/hiv-therapie/leitlinien-1/Deutsch-Osterreichilsche%20Leitlinien%20zur%20antiretroviralen%20Therapie%20der%20HIV-Infektion.pdf.

23. Mielck A, Vogelmann M, Schweikert B, Leidl R. Gesundheitszustand bei Erwachsenen in Deutschland: Ergebnisse einer repräsentativen Befragung mit dem EuroQol 5D (EQ-5D). Gesundheitswesen 2010; 72(8-9):476–86.

24. Venturini A, Giannini B, Montefiori M, Di Biagio A, Mazzarello G, Cenderello G et al. Quality of life of people living with HIV, preliminary results from IANUA (Investigation on Antiretroviral Therapy) study. J Int AIDS Soc 2014; 17(4 Suppl 3):19581.

25. Zinkernagel C, Ledergerber B, Battegay M, Cone RW, Vernazza P, Hirschel B et al. Quality of life in asymptomatic patients with early HIV infection initiating antiretroviral therapy. Swiss HIV Cohort Study. AIDS 1999; 13(12):1587–9.

26. Bing EG, Hays RD, Jacobson LP, Chen B, Gange SJ, Kass NE et al. Health-related quality of life among people with HIV disease: results from the Multicenter AIDS Cohort Study. Qual Life Res 2000; 9(1):55–63.

27. Herrmann S, McKinnon E, Hyland NB, Lalanne C, Mallal S, Nolan D et al. HIV-related stigma and physical symptoms have a persistent influence on health-related quality of life in Australians with HIV infection. Health Qual Life Outcomes 2013; 11:56.

28. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015; 373(9):795–807.

29. Préau M, Marcellin F, Carrieri MP, Lert F, Obadia Y, Spire B. Health-related quality of life in French people living with HIV in 2003: results from the national ANRS-EN12-VESPA Study. AIDS 2007; 21 Suppl 1:S19-27.

30. Jia H, Uphold CR, Zheng Y, Wu S, Chen GJ, Findley K et al. A further investigation of health-related quality of life over time among men with HIV infection in the HAART era. Qual Life Res 2007; 16(6):961–8.

31. Mahlich J, Bogner JR, Tomeczkowski J, Stoll M. Treatment strategies for treatment naïve HIV patients in Germany: evidence from claims data. Springerplus 2015; 4:306.

32. Mahlich J, Groß M, Kuhlmann A, Bogner J, Heiken H, Stoll M. The choice between a ritonavir-boosted protease inhibitor- and a non-nucleoside reverse transcriptase inhibitor-based regimen for initiation of antiretroviral treatment - results from an observational study in Germany. J Pharm Policy Pract 2016; 9:39.

33. World Health Organization. WHOQOL-HIV Instrument; 2002 [cited 2019 Aug 25]. Available from: URL: http://www.who.int/mental_health/media/en/557.pdf.

Supplement

Table S1: Socio-demographic characteristics of the patients in CORSAR. (n=participants who completed EQ-5D-3L questionnaires)

Characteristic	at Visit 0 (Baseline) (n=1056)		at Visit 1 (12 weeks) (n=808)		at Visit 2 (24 weeks) (n=754)		at Visit 3 (36 weeks) (n=707)		at Visit 4 (48 weeks) (n=682)		at Visit 5 (60 weeks) (n=672)		at Visit 6 (72 weeks) (n=669)		at Visit 7 (84 weeks) (n=667)		at Visit 8 (96 weeks) (n=721)	
Age (mean. SD)	47.6	11.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Age (n.%)																		
<20 years old	1	0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20-29 years old	43	4.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30-39 years old	207	19.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40-49 years old	444	42	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50-59 years old	223	21.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
>60 years old	138	13.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gender (n.%)																		
Male	938	88.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Female	112	10.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Transsexual	6	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Education level (n.%)																		
No qualifications	88	8.3	52	6.4	42	5.6	38	5.4	27	4	26	3.9	25	3.7	27	4	33	4.6
Secondary school leaving certificate (leaving after 9th grade)	243	23	202	25	176	23.3	165	23.3	170	24.9	165	24.6	165	24.7	171	25.6	185	25.7
Intermediate school-leaving certificate (leaving after 9th grade)	308	29.2	232	28.7	221	29.3	198	28	197	28.9	190	28.3	196	29.3	195	29.2	181	25.1
School diploma corresponding to university entrance level	195	18.5	139	17.2	142	18.8	136	19.2	139	20.4	131	19.5	132	19.7	128	19.2	142	19.7
Professional training	86	8.1	84	10.4	78	10.3	85	12	69	10.1	65	9.7	68	10.2	67	10	93	12.9
University	115	10.9	79	9.8	80	10.6	65	9.2	67	9.8	76	11.3	71	10.6	63	9.4	73	10.1
Other	3	0.3	5	0.6	1	0.1	7	1	3	0.4	3	0.4	4	0.6	3	0.4	3	0.4
No response	88	8.3	52	6.4	42	5.6	38	5.4	27	4	26	3.9	25	3.7	27	4	33	4.6
Employment status (n. %)																		
Full-time employed	418	39.6	323	40	310	41.1	268	37.9	280	41.1	271	40.3	271	40.5	268	40.2	304	42.2
Part-time employed	77	7.3	58	7.2	52	6.9	58	8.2	50	7.3	48	7.1	54	8.1	61	9.1	70	9.7

Self-employed	73	6.9	43	5.3	43	5.7	53	7.5	44	6.5	45	6.7	50	7.5	46	6.9	50	6.9
Unemployed	95	9	71	8.8	70	9.3	53	7.5	56	8.2	47	7	42	6.3	46	6.9	51	7.1
Retired	241	22.8	202	25	190	25.2	192	27.2	189	27.7	189	28.1	187	28	179	26.8	178	24.7
House	17	1.6	15	1.9	16	2.1	16	2.3	12	1.8	12	1.8	12	1.8	12	1.8	13	1.8
In study	10	0.9	6	0.7	5	0.7	4	0.6	4	0.6	7	1	8	1.2	7	1	6	0.8
Other	17	1.6	13	1.6	10	1.3	8	1.1	12	1.8	15	2.2	14	2.1	12	1.8	11	1.5
No response	108	10.2	77	9.5	58	7.7	55	7.8	35	5.1	38	5.7	31	4.6	36	5.4	38	5.3

Table S2: Health-related and clinical characteristics of the patients in CORSAR.

Characteristic	at Visit 0 (Baseline) (n=1056)		at Visit 1 (12 weeks) (n=808)		at Visit 2 (24 weeks) (n=754)		at Visit 3 (36 weeks) (n=707)		at Visit 4 (48 weeks) (n=682)		at Visit 5 (60 weeks) (n=672)		at Visit 6 (72 weeks) (n=669)		at Visit 7 (84 weeks) (n=667)		at Visit 8 (96 weeks) (n=721)	
Years since diagnosis of HIV (mean. SD)	10.7	7.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV infection stage (CDC classification) (n. %)																		
Asymptomatic (Category A)	302	28.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptomatic (Category B)	443	42	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
AIDS-Indicator (Category C)	286	27.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not recorded	25	2.4																
CD4+ cell count (n. %)																		
<200 cells/µL	65	6.2	49	6.1	33	4.4	32	4.5	24	3.5	29	4.3	23	3.4	19	2.8	23	3.2
200-499 cells/µL	402	38.1	301	37.3	283	37.5	259	36.6	235	34.5	224	33.3	230	34.4	218	32.7	236	32.7
≥500 cells/µL	585	55.4	448	55.4	435	57.7	412	58.3	420	61.6	417	62.1	416	62.2	429	64.3	462	64.1
Not recorded	4	0.4	10	1.2	3	0.4	4	0.6	3	0.4	2	0.3	0	0	1	0.1	0	0
HIV viral load (different grouping) (n. %)																		
Below quantification limit	949	89.9	727	90	694	92	660	93.4	645	94.6	641	95.4	642	96	638	95.7	677	93.9
<10.000	90	8.5	64	7.9	57	7.6	41	5.8	31	4.5	25	3.7	22	3.3	26	3.9	38	5.3
10.000-100.000	7	0.7	5	0.6	0	0	3	0.4	3	0.4	2	0.3	4	0.6	0	0	5	0.7
≥100.000	6	0.6	1	0.1	0	0	0	0	0	0	2	0.3	1	0.1	2	0.3	1	0.1
Not recorded	4	0.4	11	1.4	3	0.4	3	0.4	3	0.4	2	0.3	0	0	1	0.1	0	0

Comorbidity (n. %)																		
Presence of comorbidity	872	82.6	592	73.3	568	75.3	556	78.6	544	79.8	547	81.4	521	495	74.2	559	77.5	872
1-4 conditions	655	62	440	54.5	402	53.3	379	53.6	394	57.8	380	56.5	363	54.3	352	52.8	403	55.9
>5conditions	216	20.5	151	18.7	165	21.9	176	24.9	146	21.4	164	24.4	154	23	139	20.8	151	20.9
Allergy	188	17.8	113	14	125	16.6	123	17.4	97	14.2	108	16.1	95	14.2	99	14.8	100	13.9
Dermatological	286	27.1	204	25.2	191	25.3	199	28.1	181	26.5	186	27.7	176	26.3	162	24.3	175	24.3
Respirational	183	17.3	150	18.6	137	18.2	142	20.1	119	17.4	129	19.2	133	19.9	130	19.5	146	20.2
Cardiovascular	248	23.5	165	20.4	170	22.5	174	24.6	159	23.3	172	25.6	156	23.3	143	21.4	159	22.1
Endocrine	134	12.7	82	10.1	99	13.1	98	13.9	84	12.3	92	13.7	83	12.4	67	10	84	11.7
Gastro-intestinal	249	23.6	183	22.6	175	23.2	173	24.5	158	23.2	159	23.7	157	23.5	151	22.6	176	24.4
Haematological	89	8.4	58	7.2	57	7.6	61	8.6	48	7	52	7.7	49	7.3	44	6.6	50	6.9
Neurological	145	13.7	83	10.3	78	10.3	84	11.9	71	10.4	83	12.4	75	11.2	68	10.2	65	9
Psychiatric	209	19.8	126	15.6	144	19.1	134	19	128	18.8	143	21.3	128	19.1	115	17.2	135	18.7
Other. including :	601	56.9	415	51.4	407	54	423	59.8	399	58.5	420	62.5	387	57.8	370	55.5	426	59.1
Lipodystrophy	58	5.5	34	4.2	37	4.9	42	5.9	39	5.7	40	6	42	6.3	40	6	36	5
Diabetes mellitus	13	1.2	10	1.2	9	1.2	10	1.4	7	1	10	1.5	5	0.7	6	0.9	7	1
Hepatitis C	35	3.3	25	3.1	22	2.9	23	3.3	24	3.5	22	3.3	26	3.9	21	3.1	28	3.9
Hepatitis B	52	4.9	36	4.5	29	3.8	34	4.8	26	3.8	32	4.8	33	4.9	23	3.4	24	3.3
Depression	8	0.8	0	0	0	0	0	0	0	0	1	0.1	3	0.4	0	0	2	0.3

Table S3. Therapy characteristics in patients of CORSAR (n=1034).

Characteristics	n	%
Prescribed regimen at baseline	1034	
PI based regimen:		
regimen "PI stand", most prescribed *PIs* + NRTIs regimen included:	408	*100*
Atazanavir/Emtricitabin&Tenofovir/*Ritonavir*/	81	19.9
Darunavir/Emtricitabin&Tenofovir/*Ritonavir*/	51	12.5
Emtricitabin&Tenofovir/*Lopinavir(tbl)*/	34	8.3
Emtricitabin&Tenofovir/*Lopinavir(cps)*/	29	7.1
Emtricitabin&Tenofovir/*Fosamprenavir* /*Ritonavir*/	23	5.6
Emtricitabin&Tenofovir/*Ritonavir*/*Saquinavir-Invirase*/	16	3.9
Abacavir&Lamivudin/*Atazanavir*/*Ritonavir*/	18	4.4
Abacavir&Lamivudin/*Fosamprenavir* /*Ritonavir*/	13	3.2
Abacavir&Lamivudin/*Darunavir*/*Ritonavir*/	10	2.5
regimen "PI ind". most prescribed regimen included	106	
Lopinavir (Tbl.)/Saquinavir-Invirase/	6	5.7
NNRTI based regimen		
regimen "NNRTI stand", most prescribed *NNRTIs*+NRTIs regimen included:	280	*100*
Emtricitabin&Tenofovir/*Nevirapin*/	103	36.8
Abacavir&Lamivudin/*Nevirapin*/	34	12.1
Abacavir&Lamivudin/*Efavirenz*/	31	11.1
Efavirenz/Emtricitabin&Tenofovir/	32	11.4
Efavirenz/Lamivudin&Zidovudin/	8	2.9
Lamivudin&Zidovudin/*Nevirapin*/	22	7.9
regimen "NNRTI ind", most prescribed regimen included:	12	
Efavirenz/Emtricitabin&Tenofovir&*Efavirenz*/	2	16.7
NRTI based regimen	228	*100*
Emtricitabin&Tenofovir&Efavirenz/ (*NRTIs*+NNRTI)	157	68.9
Abacavir&Lamivudin&Zidovudin/ (*NRTIs*)	15	6.6
Emtricitabin&Tenofovir/Raltegravir/ (*NRTIs* + INSTI)	13	5.7
Abacavir&Lamivudin&Zidovudin/*Tenofovir*/ (*NRTIs*)	5	2.2
Abacavir&Lamivudin/(*NRTIs*)	5	2.2

Table S3.1: cART substances and class.

Substances:	Class
Abacavir	NRTI
Abacavir&Lamivudin	NRTI
Abacavir&Lamivudin&Zidovudin	NRTI
Amprenavir	PI
Atazanavir	PI
Darunavir	PI
Delaviridin	NNRTI
Didanosin	nRTI
Efavirenz	NNRTI
Emtricitabin	NRTI
Emtricitabin&Tenofovir	NRTI
Emtricitabin&Tenofovir&Efavirenz	NRTIs and NNRTI
Enfuvirtid	FI
Etravirin	NNRTI
Fosamprenavir	PI
Hydroxyurea	other
Indinavir	PI
Lamivudin	NRTI
Lamivudin&Zidovudin	NRTI
Lopinavir (Kps.)	PI
Lopinavir (Tbl.)	PI
Maraviroc	other
Nelfinavir	PI
Nevirapin	NNRTI
Raltegravir	INSTI
Ritonavir	PI
Saquinavir-Fortovase	PI
Saquinavir-Invirase	PI
Stavudin	NRTI
Tenofovir	NRTI
Tipranavir	PI
Zalcitabin	NRTI
Zidovudin	NRTI

Table S4: Records of measurement of quality of life of the patients in CORSAR.

Characteristic	at Visit 0 (Baseline) (n=1056)		at Visit 1 (12 weeks) (n=808)		at Visit 2 (24 weeks) (n=754)		at Visit 3 (36 weeks) (n=707)		at Visit 4 (48 weeks) (n=682)		at Visit 5 (60 weeks) (n=672)		at Visit 6 (72 weeks) (n=669)		at Visit 7 (84 weeks) (n=667)		at Visit 8 (96 weeks) (n=721)	
Most reported health states at baseline (n.*% of total*)																		
11111	479	45.4	356	44.1	344	45.6	337	47.7	306	44.9	312	46.4	308	46	311	46.6	339	47
11112	111	10.5	88	10.9	71	9.4	65	9.2	66	9.7	62	9.2	68	10.2	57	8.5	57	7.9
11121	96	9.1	89	11	86	11.4	69	9.8	74	10.9	68	10.1	65	9.7	70	10.5	86	11.9
11122	96	9.1	66	8.2	72	9.5	69	9.8	67	9.8	60	8.9	63	9.4	63	9.4	63	8.7
11212	13	1.2	5	0.6	6	0.8	7	1	7	1	5	0.7	4	0.6	6	0.9	7	1
11221	16	1.5	16	2	16	2.1	6	0.8	11	1.6	11	1.6	7	1	7	1	5	0.7
11222	46	4.4	35	4.3	22	2.9	18	2.5	26	3.8	19	2.8	22	3.3	21	3.1	23	3.2
21121	26	2.5	20	2.5	18	2.4	25	3.5	22	3.2	22	3.3	22	3.3	19	2.8	26	3.6
21122	21	2	19	2.4	9	1.2	17	2.4	15	2.2	18	2.7	22	3.3	19	2.8	11	1.5
21221	20	1.9	13	1.6	7	0.9	7	1	11	1.6	15	2.2	13	1.9	6	0.9	9	1.2
21222	36	3.4	28	3.5	29	3.8	19	2.7	20	2.9	24	3.6	21	3.1	28	4.2	29	4
EQ-5D-3L domains (n.%)																		
Mobility problems																		
None	885	83.8	679	84	645	85.5	595	84.2	574	84.2	551	82	548	81.9	548	82.2	603	83.6
Some	171	16.2	128	15.8	108	14.3	112	15.8	108	15.8	121	18	121	18.1	119	17.8	117	16.2
Severe	0	0	1	0.1	1	0.1	0	0	0	0	0	0	0	0	0	0	1	0.1
Problems with self-care																		
None	1032	97.7	782	96.8	733	97.2	678	95.9	656	96.2	643	95.7	642	96	638	95.7	693	96.1
Some	23	2.2	22	2.7	19	2.5	28	4	23	3.4	28	4.2	26	3.9	28	4.2	28	3.9
Severe	1	0.1	4	0.5	2	0.3	1	0.1	3	0.4	1	0.1	1	0.1	1	0.1	0	0
Problems performing usual activities																		
None	857	81.2	659	81.6	620	82.2	596	84.3	563	82.6	550	81.8	560	83.7	558	83.7	601	83.4
Some	187	17.7	145	17.9	127	16.8	107	15.1	116	17	119	17.7	107	16	107	16	118	16.4
Severe	12	1.1	4	0.5	7	0.9	4	0.6	3	0.4	3	0.4	2	0.3	2	0.3	2	0.3
Pain/discomfort																		
None	632	59.8	471	58.3	444	58.9	433	61.2	398	58.4	390	58	393	58.7	387	58	421	58.4

Some	395	37.4	320	39.6	291	38.6	262	37.1	269	39.4	267	39.7	259	38.7	264	39.6	286	39.7
Severe	29	2.7	17	2.1	19	2.5	12	1.7	15	2.2	15	2.2	17	2.5	16	2.4	14	1.9
Anxiety/depression																		
None	664	62.9	520	64.4	492	65.3	464	65.6	446	65.4	441	65.6	428	64	431	64.6	484	67.1
Some	366	34.7	265	32.8	242	32.1	222	31.4	219	32.1	216	32.1	227	33.9	221	33.1	212	29.4
Severe	26	2.5	23	2.8	20	2.7	21	3	17	2.5	15	2.2	14	2.1	15	2.2	25	3.5
TTO utility value (n.%)																		
Mean. SD	0.912	0.154	0.911	0.153	0.91	0.157	0.917	0.142	0.913	0.15	0.911	0.149	0.911	0.153	0.911	0.149	0.91	0.152
0.0-0.2	7	0.7	8	1	4	0.5	4	0.6	6	0.9	8	1.2	7	1	6	0.9	6	0.8
0.2-0.4	26	2.5	13	1.6	23	3.1	10	1.4	13	1.9	8	1.2	13	1.9	11	1.6	14	1.9
0.4-0.6	19	1.8	17	2.1	16	2.1	14	2	8	1.2	11	1.6	7	1	10	1.5	15	2.1
0.6-0.8	121	11.5	94	11.6	73	9.7	87	12.3	80	11.7	98	14.6	95	14.2	91	13.6	90	12.5
0.8-0.9	257	24.3	210	26	200	26.5	168	23.8	183	26.8	162	24.1	160	23.9	166	24.9	181	25.1
0.9-1.0	626	59.3	466	57.7	438	58.1	424	60	392	57.5	385	57.3	387	57.8	383	57.4	415	57.6
VAS score (n.%)																		
Mean. SD	84.32	18.55	84.45	18.26	84.76	18.63	85.39	18.08	84.92	17.95	84.97	18.2	84.83	18.17	84.93	18.22	85.28	18.47
0-20	5	0.5	6	0.7	4	0.5	5	0.7	7	1	4	0.6	4	0.6	4	0.6	3	0.4
20-40	43	4.1	29	3.6	31	4.1	21	3	16	2.3	21	3.1	21	3.1	16	2.4	28	3.9
40-60	21	2	15	1.9	19	2.5	19	2.7	14	2.1	20	3	18	2.7	26	3.9	16	2.2
60-80	373	35.3	283	35	239	31.7	224	31.7	237	34.8	222	33	228	34.1	215	32.2	215	29.8
80-90	39	3.7	30	3.7	31	4.1	32	4.5	28	4.1	25	3.7	25	3.7	25	3.7	34	4.7
90-100	575	54.5	445	55.1	430	57	406	57.4	380	55.7	380	56.5	373	55.8	381	57.1	425	58.9

Article 6

Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting

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Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting

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Abstract

Background: In lung cancer screening, a nodule management protocol describes nodule assessment and thresholds for nodule size and growth rate to identify patients who require immediate diagnostic evaluation or additional imaging exams. The Netherlands-Leuvens Screening Trial and the National Lung Screening Trial used different selection criteria and nodule management protocols. Several modelling studies have reported variations in screening outcomes and cost-effectiveness across selection criteria and screening intervals; however, the effect of variations in the nodule management protocol remains uncertain. This study evaluated the effects of the eligibility criteria and nodule management protocols on the benefits, harms and cost-effectiveness of lung screening scenarios in a population-based setting in Germany.

Methods: We developed a modular microsimulation model: a biological module simulated individual histories of lung cancer development from carcinogenesis onset to death; a screening module simulated patient selection, screening-detection, nodule management protocols, diagnostic evaluation and screening outcomes. Benefits included mortality reduction, life years gained and averted lung cancer deaths. Harms were costs, false positives and overdiagnosis. The comparator was no screening. The evaluated 76 screening scenarios included variations in selection criteria and thresholds for nodule size and growth rate.

Results: Five years of annual screening resulted in a 9.7–12.8% lung cancer mortality reduction in the screened population. The efficient scenarios included volumetric assessment of nodule size, a threshold for a volume of 300 mm^3 and a threshold for a volume doubling time of 400 days. Assessment of volume doubling time is essential for reducing overdiagnosis and false positives. Incremental cost-effectiveness ratios of the efficient scenarios were 16,754–23,847 euro per life year gained and 155,287–285,630 euro per averted lung cancer death.

Conclusions: Lung cancer screening can be cost-effective in Germany. Along with the eligibility criteria, the nodule management protocol influences screening performance and cost-effectiveness. Definition of the thresholds for nodule size and nodule growth in the nodule management protocol should be considered in detail when defining optimal screening strategies.

Keywords: LDCT lung screening, Lung cancer, NELSON, NLST, Nodule management protocol, Cost-effectiveness

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Background

The National Lung Screening Trial (NLST) in the USA [1] has shown that lung screening with low-dose computed tomography (LDCT) can reduce lung cancer mortality by 20%, but it also can induce harms that the screened population may experience, i.e. false-positive findings, overdiagnosed cases, radiation-related deaths and interval cancers [2–5]. The largest lung screening trial in Europe, the Netherlands-Leuvens Screening Trial (NELSON) [6], used less stringent selection criteria and a different approach to patient management and has reported a reduced number of false positives compared to NLST [7]. The nodule management protocols of NLST and NELSON differ in applied measurement techniques (diametric vs volumetric assessment), follow-up algorithms and the definition of a cut-off nodule size indicating a cancer-positive result [8]. However, other differences between the studies (e.g. screened cohort, screening intervals) make it difficult to recognise the potential of nodule management approaches to succeed in the reduction of harms of screening.

Designing a screening program with an optimal balance between the benefits, harms and/or cost-effectiveness has become a major challenge for healthcare decision-makers who manage development of a lung screening program and decide on population selection strategies and screening intervals [7, 9, 10] as well as for clinicians who decide how to manage a screening-detected lung nodule [7].

Several modelling studies have examined trade-offs between the benefits and harms of LDCT screening and contributed to comprehension of the effects that eligibility criteria and screening intervals might have on its long-term screening performance and cost-effectiveness [11–18]. However, the effects of nodule management strategies have not been investigated in detail, and our understanding of how to proceed with a screening-detected nodule remains limited [19]. An algorithm for nodule assessment and management determines ways to prognosticate malignancy, defines core procedures of a screening program and may strongly influence the screening outcomes [20].

In this modelling study, we aimed to investigate the effects of the eligibility criteria and nodule management on the benefits, harms and cost-effectiveness of lung screening with LDCT in a population-based setting.

Methods

Microsimulation model

We developed a stochastic modular microsimulation model that simulated individual life histories focusing on the development of lung cancer and its progression from the onset of the first malignant cell to death from lung cancer.

The model consists of the following structural modules: population, natural history, clinical detection, survival, screening and life history (Fig. 1). The model was populated with 10% of the German population aged 40 years and older. Data on smoking behaviour was obtained from the German Health Update (GEDA) survey (years 2009–2012) [21], and the demographic structure of 2012 was obtained from the German statistical office [22].

The natural history module contains a biological two-stage clonal expansion (TSCE) model [23] and a tumour growth component and simulates a complete flow of events in the development of lung cancer (details are available in Additional file 1: Section 1.1.2). The TSCE model defines the individual age at the onset of the first malignant cell and the histologic cancer type: small cell, large cell, squamous cell carcinoma, adenocarcinoma or adenocarcinoma in situ (AIS). The progression of lung cancer is described via tumour growth, lymph nodes involvement and metastasis. The tumour growth is defined by a Gompertz function [24] (Additional file 1: Section 1.1.4.2). This function describes the relation between time and the tumour volume. For a specific tumour volume the function gives the time needed to reach this volume and vice versa. The module uses the age at the onset of the first malignant cell and the time to reach the stage-specific volume and gives the age at different stages of the progression of the disease. Threshold tumour volumes at the stages of nodal involvement, distant metastases and clinical diagnosis are randomly drawn from log-normal distributions (Additional file 1: Table S5), and the tumour growth model is applied to calculate the corresponding ages of the individual. The clinical detection module determines the stage of lung cancer (I, II, III, IV) according to the tumour-node-metastasis (TNM) staging system based on the tumour volume and spread (local, nodal involvement, distant metastasis) at the age of diagnosis (Additional file 1: Section 1.1.3).

The lung cancer survival is modelled as long-term survival, which lets the individual live until death from other causes, and short-term survival in years, which follows the Weibull distribution [25]. The parameters vary over the histological classes and stages at the time of diagnosis (Additional file 1: Table S1, Section 1.1.3) [25].

The screening module (Additional file 1: Section 1.1.5) contains several structural components: eligibility assessment, screening-detection, nodule management (including follow-up), diagnostic work-up and lung cancer survival. For each individual it creates a screening schedule based on eligibility criteria and nodule management protocol. At each screening exam, the module checks for presence of a lung nodule and determines its volume using the tumour growth function, the individual's age and the age at the onset of the first malignant cell. Screening-detection depends

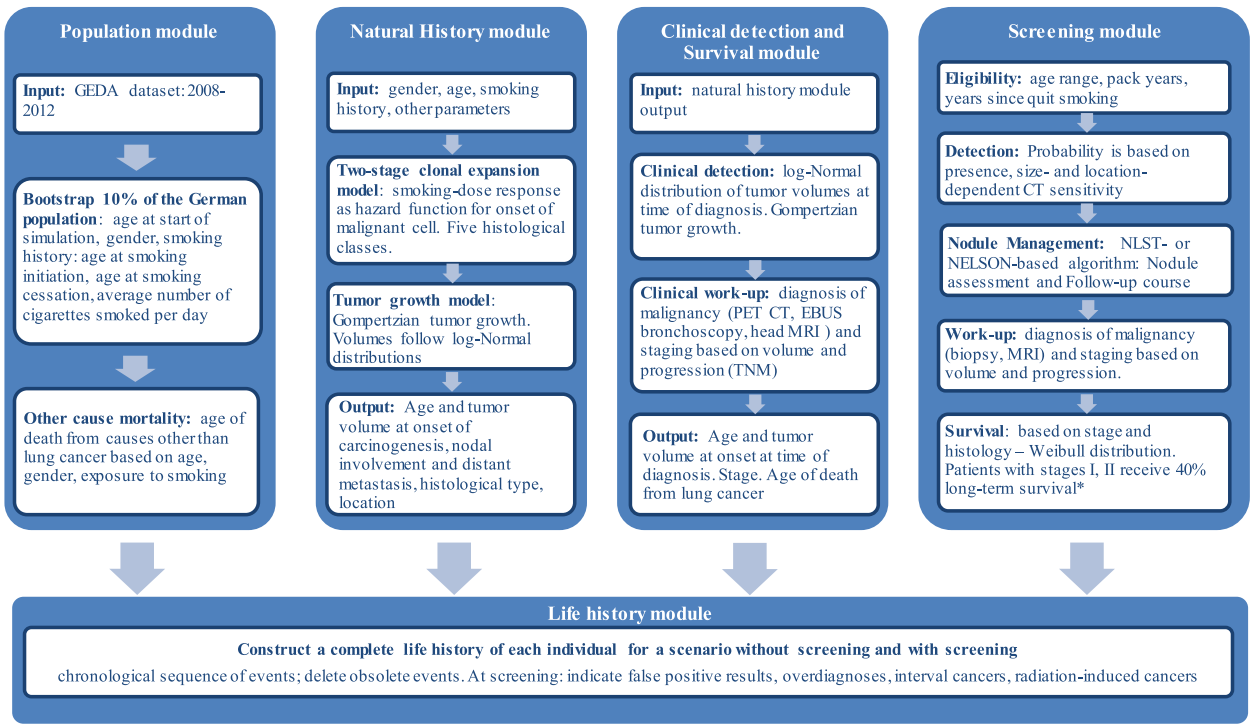

Fig. 1 Structural modules of the microsimulation model. * refers to the case in which the patients would die from lung cancer in the no screening scenario

on the location and volume of the tumour and the sensitivity of the CT scan (Additional file 1: Section 1.1.5.2, Table S7). Individuals with a detected nodule proceed with a nodule management algorithm. The nodule management algorithm defines the threshold values of the nodule size and tumour growth and indicates the patients who require immediate diagnostic work-up or undergo additional imaging exams (follow-up course).

Two nodule management algorithms were designed based on those used in the NELSON and NLST trials. Schematic representations of the algorithms are given in Figs. 2 and 3. The modelled NELSON-like nodule management algorithm includes volumetric assessment of the nodule size. Based on the nodule volume, the patients undergo either the next screening round (if negative), a follow-up exam 3 months later (if indeterminate) or an immediate diagnostic evaluation (if positive) [6, 26]. At the follow-up examination, tumour growth and tumour volume doubling time (VDT [6]) are assessed as an additional malignancy predictor.

The NLST-like nodule management algorithm includes diametric assessment of the nodule size and defines three categories of screening results: negative, positive intermediate and positive (Fig. 3). In contrast to the NELSON-like nodule management algorithm, individuals with positive intermediate initial results undergo a course of follow-up chest imaging exams where tumour growth is assessed as a change (%) in the nodule diameter relative to the result at the initial screening. The follow-up can occur with a fixed periodicity: at 3, 6 and 12 months after the initial screening. Additional details on the modelled nodule management protocols are available in Additional file 1: Section 1.1.5.3. Individuals with lung cancer, defined in the management algorithm, undergo the diagnostic work-up component (Additional file 1: Section 1.1.5.4), and the tumour is staged according to TNM classification based on the volume and spread. These patients are withdrawn from the regular screening schedule.

We assume that individuals with screen-detected lung cancer live at least as long as they would in the no screening scenario. In the screening module lung cancer, survival component alters the age of death from lung cancer for the persons with a screen-detected lung cancer at stages I and II: if they die from lung cancer in the no screening scenario, they receive 40% probability of long-term survival [25]. The screening module sums up imaging exams, work-ups, complications and treatments. The life history module computes false positives and interval cancers and calculates overdiagnosed cases and deaths from radiation-induced cancer (Additional file 1: Section 1.1.6). Figure 4 gives a schematic representation of the modelling of the tumour growth and interaction between the natural history, screening, clinical diagnosis and survival modules.

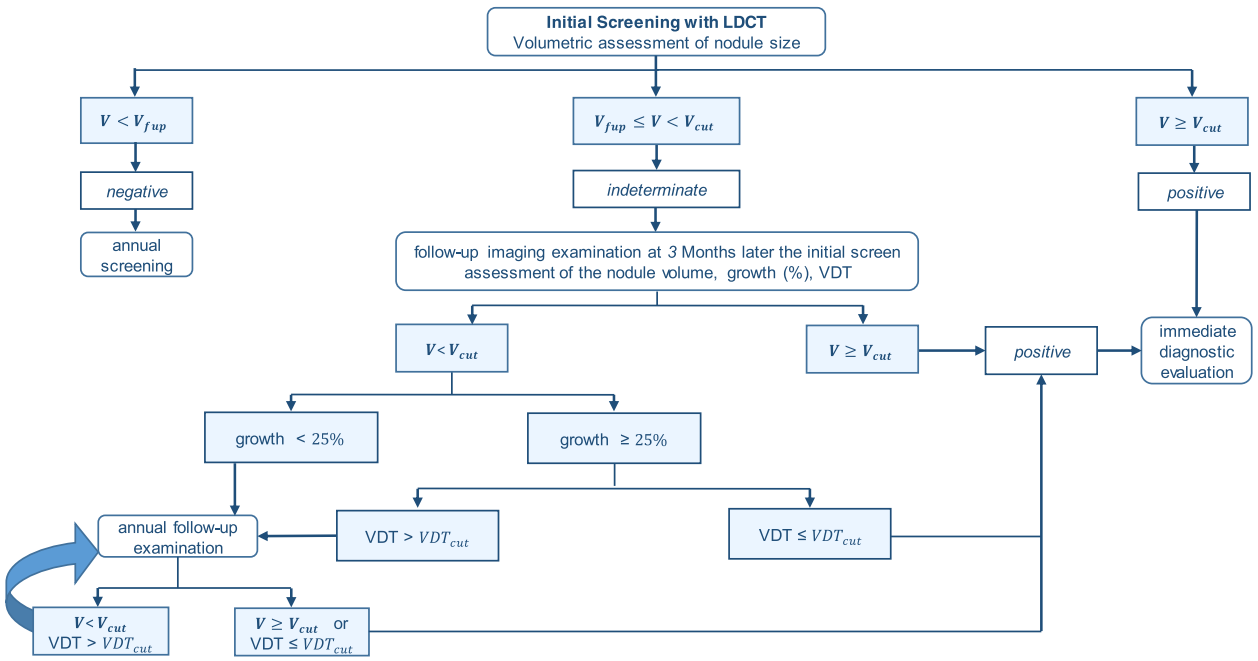

Fig. 2 Schematic representation of modelled NELSON-like nodule management protocol. V_{cut} and VDT_{cut} indicate the threshold values of the volume and volume doubling time which indicate a cancer positive result. V_{fup} represents low threshold volume for a follow-up examination

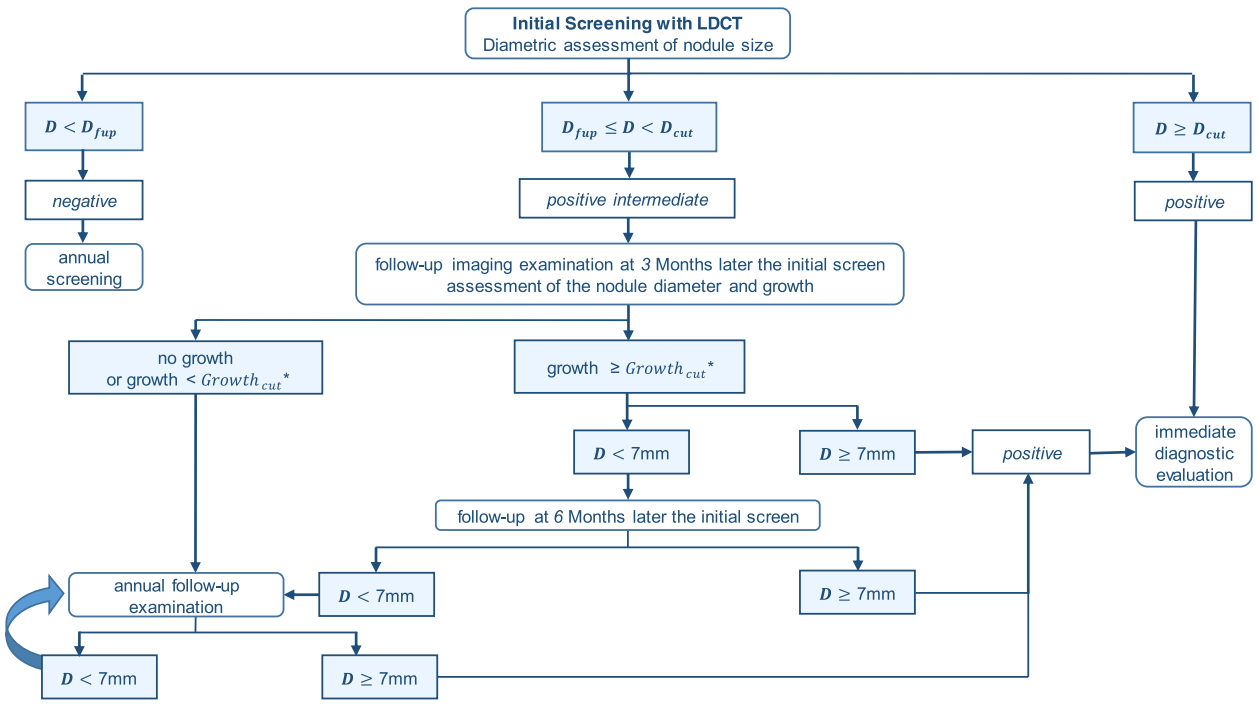

Fig. 3 Schematic representation of modelled NLST-like nodule management protocol. *Growth is calculated as a percentage increase in the diameter vs the diameter at the initial screening. D_{cut} and $Growth_{cut}$ indicate the threshold values of the diameter and percentage increase in the diameter that indicate a cancer positive result. D_{fup} represents low threshold diameter for a follow-up examination

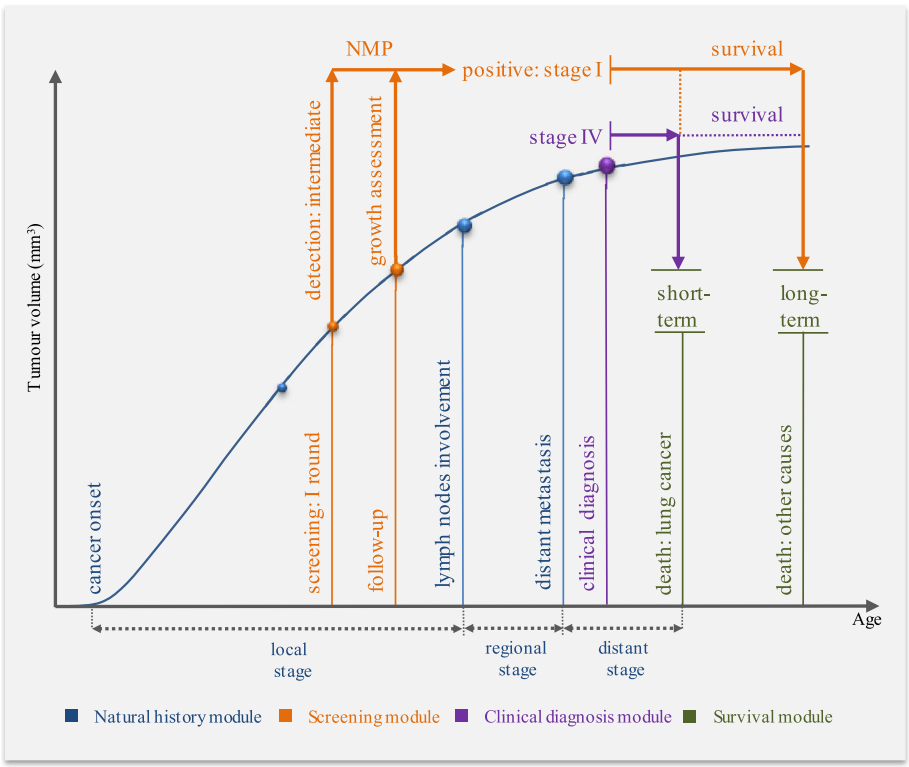

Fig. 4 Schematic representation of modelled tumour growth and interaction between the natural history, screening, clinical diagnosis and survival modules. *NMP* nodule management protocol. The curve schematically represents the tumour growth. Figure does not reflect the scales. The natural history module contains a biological two-stage clonal expansion (*TSCE*) model and a tumour growth component and simulates for each individual the age at the onset of carcinogenesis, its histological features, the age and tumour size at the lymph nodes involvement and distant metastasis. The TSCE model simulates age at the cancer onset for each histological class. The final histological class for the individual is determined based on the competing risk (the lowest age at onset). The tumour growth component applies a Gompertz function which describes the relation between time (age) and the tumour volume. The clinical diagnosis model determines the age at lung cancer diagnosis and stage of the tumour according to TNM classification using the tumour growth model and information on the tumour progression from the natural history module. The screening module simulates an individual screening schedule based on the eligibility criteria. It applies the tumour growth module to determine the tumour volume at age of screening and uses information on the tumour progression for staging the screen-detected tumour according to TNM classification. The survival model determines the age of death based on the tumour stage and histological class. The figure illustrates a case where an individual in the no screening scenario develops a lung cancer tumour and is eventually symptomatically diagnosed with lung cancer at stage IV. The patient dies from lung cancer in the no screening scenario. In the screening scenario, a nodule (tumour) is detected in the first round of screening. The screen-detected nodule is small for the patient to undergo an immediate diagnostic evaluation. The patient undergoes a follow-up exam, where the growth is assessed according to the NMP. The growth and/or the volume doubling time meet the definition of cancer according to the NMP. The screen-detected tumour is at the local stage, and the patient is diagnosed with lung cancer at stage I in the screening scenario. The patient is cured and dies from other causes. The model calculates life years gained for each individual in the screened cohort

Screening scenarios

At base case, a 5-year LDCT annual lung screening program with perfect adherence was evaluated. Overall, 76 scenarios were constructed using variations of the eligibility criteria (four different screened populations) and nodule management protocol (defined as the NELSON-like or NLST-like protocol) (Table 1). The outcomes were projected over the course of a lifetime. Lung cancer-specific mortality reduction and false-positive cases were calculated for the screened cohort.

Health economics

Costs included LDCT exams, staging tests and lifetime treatment (Additional file 1: Table S8). Expenditures of lifetime treatment, due to limitations of available cost data for Germany, were calculated via application of cost variations across cancer stages obtained from the UK cost data [27] compared with the German cost data [28] (Additional file 1: Section 1.3). The lifetime treatment costs for patients with early-stage and advanced cancers were 45,803 euro for stages I/II and 30,101 euro for stages III/IV.

Table 1 Characteristics of the evaluated screening scenarios

Characteristics	Considered variations
Eligibility criteria	
Population:	50-74-30-15
Values arranged as	(eligibility criteria of the NLST clinical trial)
age at begin smoking - age at quit smoking - minimum pack years - maximum years since quitting smoking	55-80-30-15
	(as recommended by the US Preventive Services Task Force (USPSTF) for lung screening with LDCT [2])
	50-75-15-9
	(less restrictive eligibility criteria, similar to the NELSON trial)
	55-75-40-10
	(more restrictive eligibility criteria) [18]
Nodule management algorithm	
NELSON-like	VDT_{cut} = 400 days – V_{cut} = 500 mm^3
Scenario is characterised by the threshold value of the volume doubling time (VDT_{cut}) and the cut-off volume (V_{cut}) for cancer positive	(values of the NELSON clinical trial)
	VDT_{cut} = 400 days – VDT_{cut} = 300 mm^3
	VDT_{cut} = 400 days – VDT_{cut} = 400 mm^3
	VDT_{cut} = 400 days – VDT_{cut} = 750 mm^3
	VDT_{cut} = 300 days – VDT_{cut} = 500 mm^3
	VDT_{cut} = 600 days – VDT_{cut} = 500 mm^3
	VDT_{cut} = 300 days – omitting VDT_{cut} [a]
	VDT_{cut} = 400 days – omitting VDT_{cut} [a]
	VDT_{cut} = 600 days – omitting VDT_{cut} [a]
	V_{fup} = 80 mm^3 – VDT_{cut} = 400 days – VDT_{cut} = 500 mm^3 [b]
NLST-like	$Growth_{cut}$ = 10% – D_{cut} = 10 mm
Scenario is characterised by the threshold value of the tumour growth and the diameter (D_{cut}) for cancer positive	(values of the NLST clinical trial)
	$Growth_{cut}$ = 10% – D_{cut} = 9 mm
	$Growth_{cut}$ = 10% – D_{cut} = 11 mm
	$Growth_{cut}$ = 7.5% – D_{cut} = 10 mm
Tumour growth (threshold growth, $Growth_{cut}$) is defined as a percentage increase in diameter	$Growth_{cut}$ = 12.5% – D_{cut} = 10 mm
	$Growth_{cut}$ = 7.5% – omitting D^a_{cut}
	$Growth_{cut}$ = 10% – omitting D^a_{cut}
	$Growth_{cut}$ = 12.5% – omitting D^a_{cut}
	D_{fup} = 5 mm – Growth = 10% – D_{cut} = 10 mm [b]

[a] In these scenarios nodule growth is taken as a single malignancy predictor
[b] In these scenarios a higher nodule size for the follow-up exams (V_{fup}; D_{fup}) is used according to the British Thoracic Society guidelines [29]. In other scenarios the value of nodule size for follow-up exams is applied according to the trials as 4 mm (NLST-like) and 50 mm^3 (NELSON-like)

Cost-effectiveness was represented by average and incremental cost-effectiveness ratios (ACER and ICER, respectively). Life years gained (LYG) and averted lung cancer deaths constituted the main benefits of the screening. We applied equal (3%) and differential (3% for costs and 1.5% for LYG) annual discounting. A health insurance perspective was used.

Sensitivity analyses

One-way sensitivity analyses were performed to assess variations of the cost-effectiveness after altering assumptions about LDCT sensitivity parameters, parameters of long-term survival after screening, attendance rate cost per CT exam and lifetime treatment costs (Additional file 1: Section 1.4).

Results

Benefits and harms of screening

Annual screening led to a 9.7–12.8% reduction in lung cancer mortality in the screened cohorts. Relative to usual care, where 79% of cancers were diagnosed at stages III and IV, a screening program shifted the majority of diagnoses towards the early-staged cancers (stages I/II accounted for 66.4–71.7%). Adenocarcinomas (around

50%), squamous cell carcinomas (around 23.4%) and AIS (around 18.2%) constituted the majority of screening-detected cancers. Around 77.2% of screening-diagnosed AIS were overdiagnosed cases. Overdiagnoses constituted 9–21.5% of all screening-detected lung cancers. Small cell carcinomas were rarely detected at screening (around 5.35%) but constituted 56% of all interval cancers. False-positive diagnoses constituted 59.4–96% of all screening findings.

Eligibility criteria have a considerable influence on the main outcomes of a large-scale screening program. Evaluated scenarios with a selection of people similar to the eligibility criteria of the NLST clinical trial (55-74-30-15) gained 192,147–240,626 life years (ranged over the variations of the nodule management protocol) and 20,335–25,467 averted deaths due to lung cancer and induced 3780–5069 million euro costs additional to no screening. The scenarios with the increased threshold of exposure to smoking (40 pack-years and maximum 10 years since quitting) limited the screened population and yielded around 31% less LYG (133,222–164,864) and 29% less averted deaths (14,373–17,889) and induced 37% fewer costs (2231–3178 million euro). Increasing the stopping age to 80 (55-80-30-15) yielded around 8.3% additional LYGs (207,468–260,807) and 14.4% more averted lung cancer deaths (23,029–29,165) compared to the 55-74-30-15 scenarios and a slightly increased reduction in lung cancer mortality (12.4%); however, it induced around 13.5% more costs (4159–5811 million euro) and the highest rate of overdiagnosis. Scenarios with the least restrictive eligibility criteria, 50-75-15-9, resulted in 50.5% more LYGs (295,093–362,039) and 45.6% more averted lung cancer deaths (30,147–37,075) vs the 55-74-30-15 scenarios; however, they led to 57% more healthcare costs (6447–8026 million euro additional to no screening) and a higher number of CT scans.

Generally, the scenarios with the NELSON-like nodule management protocol resulted in 1.1–1.3% fewer lung cancer findings, but around 2.3% more findings of cancer at an early stage, 3.3–3.4% more cases of averted lung cancer deaths, around 3% more LYGs, 0.1–0.9% fewer overdiagnosed cases and around 3% more interval cancers than the NLST-like strategies. The NLST-like scenarios yielded around 51–57.4% more follow-ups of malignant nodules and considerable additional costs.

Overall, across the evaluated 76 scenarios, a few tendencies in the effects of the nodule management protocols could be seen: (1) increasing the threshold for nodule size for a cancer-positive diagnosis slightly decreased overdiagnosis, LYG and averted lung cancer deaths; (2) decreasing the cut-off size yielded more overdiagnosed cases but did not improve numbers of LYG and averted lung cancer deaths; (3) altering threshold values for a cancer indicating nodule growth when the cut-off volume stayed the same did not appreciably change the rates of LYG and averted lung cancer deaths; (4) application of VDT or an increase in diameter as a single malignancy predictor in the two-step framework remarkably reduced the accuracy of lung cancer diagnosis, but it also notably decreased rates of overdiagnosis. Increasing the threshold nodule size for a follow-up in the NELSON-like scenarios from a volume of 50 mm^3 to 80 mm^3 and in the NLST-like scenarios from a diameter of 4 mm to 5 mm, as recommended by the British Thoracic Society [29], led to a 5% and 4% decrease in overdiagnosis and a 3.7–5% decline in LYG and averted lung cancer deaths.

Cost-effectiveness of screening

ACER ranged from 16,754 to 24,160 euro/LYG (Fig. 5) and from 155,287 to 230,678 euro/averted lung cancer death (Fig. 6). Out of the 76 evaluated scenarios, three scenarios were judged to be efficient based on their cost/LYG ratio and five scenarios based on their cost per averted lung cancer death ratio (Table 2).

The scenarios that featured NELSON and NLST clinical trials were less efficient (Figs. 4 and 5, NLST- and NELSON-resembling scenarios). Compared to the NELSON-like scenarios, NLST-based screening over 5 years of annual screening would result in considerably more total costs (around 450 million euro) while yielding around 800 fewer averted deaths. Considering the cost per life year gained ratio, characteristics of the not-dominated scenario included the most restrictive eligibility criteria (55-74-40-10) and the NELSON-like nodule management protocol which applies the assessment of VDT 3 months after the initial screening as a sole malignancy predictor (Scenario 65, Table 2). The scenario yielded an ICER of 16,754 euro/LYG. The second efficient scenario (Scenario 60, Table 2) combined the threshold VDT of 400 days and a cut-off nodule volume of 300 mm^3. This scenario gained 31,642 additional life years for an incremental cost of 19,707 euro/LYG. The third efficient scenario (Scenario 41, Table 2) applied the same nodule management protocol and less stringent eligibility criteria (50-75-15-9). It gained an additional 197,174 life years for an incremental cost of 23,837 euro/LYG.

Two of the five scenarios, which were judged to be efficient based on averted cancer deaths, included the most restrictive selection criteria (55-75-40-10) and assessment of VDT 3 months later than the initial screening as a sole malignancy predictor for individuals with initial findings over 50 mm^3 in volume (Scenarios 64 and 65, Table 2). The scenario with the lowest ICER of 155,287 euro per averted death (Scenario 65 with threshold VTD of 300 days) yielded 14,373 averted deaths. Increasing the threshold value of VDT to 400 days gained an additional 1000 averted deaths for an incremental cost of 161,124 euro (Scenario 64). The inclusion of the

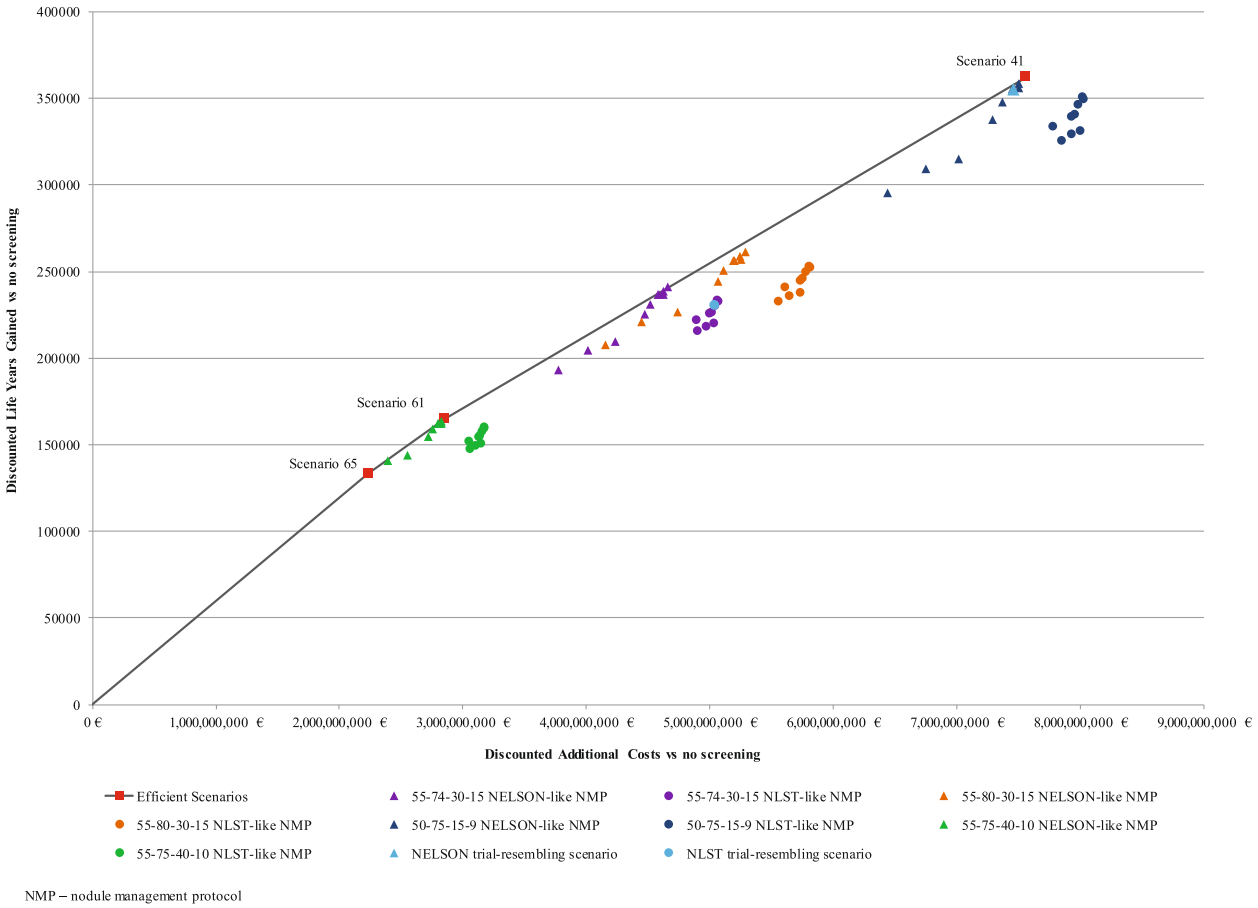

Fig. 5 The cost-effectiveness (cost per life year gained) of all evaluated scenarios and the scenarios that constitute an efficient frontier. The figure illustrates three scenarios judged to be efficient based on the cost per life year gained ratio. These scenarios constitute the efficient frontier. The other 73 evaluated scenarios are illustrated according to the population selection criteria and applied nodule management protocol (*NMP*). The figure illustrates the four evaluated eligibility criteria in different colours: 55-75-40-10 is given in *green*, 55-74-30-15 is given in *violet*, 55-80-30-15 is given in *orange* and 50-75-15-9 is given in *dark blue*. The scenarios which apply the NLST-like nodule management are illustrated with a *circular shape*. The scenarios which apply the NELSON-like nodule management are illustrated with a *triangular shape*. The figure does not specify in colour or a shape the evaluated variations of the threshold values for the tumour size and growth in the NELSON-like and NLST-like scenarios. The scenarios which resemble the eligibility criteria and nodule management protocols of the NLST and NELSON clinical trials are illustrated in *light blue*. Descriptions of the scenarios are given in Table 1. Main outcomes and cost-effectiveness of the 76 baseline screening scenarios are given in Additional file 1: Table S12

cut-off volume of 300 mm^3 (Scenario 60) into the nodule management algorithm yielded 2500 more averted deaths for an incremental cost of 184,009 euro. The scenario with less restrictive selection criteria of exposure to smoking and the increased stopping age (55-80-30-15, Scenario 22) yielded 11,276 more averted lung cancer deaths for an ICER of 216,454 vs the previous efficient scenario. The scenario with the largest number of LYG (Scenario 41) is also the scenario with the largest yield of averted cancer deaths (37,075) for an ICER of 285,630 euro per averted death.

Sensitivity analyses

Figure 7 illustrates the discounted life years and additional costs (vs no screening) for the three efficient scenarios (Scenarios 65, 60 and 41) and for their variations in the sensitivity analyses. The main cost-effectiveness drivers are cost per CT exam, treatment costs and lung cancer long-term survival probability in screening. Relative to the baseline long-term survival probability (40%), its reduction to 20% led to a more than 50% reduction in LYG and averted deaths with a more than 100% increase in cost/LYG. Increase in cost per CT exam would have a stronger adverse effect on the cost-effectiveness if the less restrictive eligibility criteria were used. More expensive treatment with innovative targeted medication at a lifetime cost of 77,702 euro [28] would increase the ACER by 65%. An increase of the CT sensitivity for smaller nodules would slightly improve the cost-effectiveness; a 20% decrease of the sensitivity would lead to a more than 10% increase in

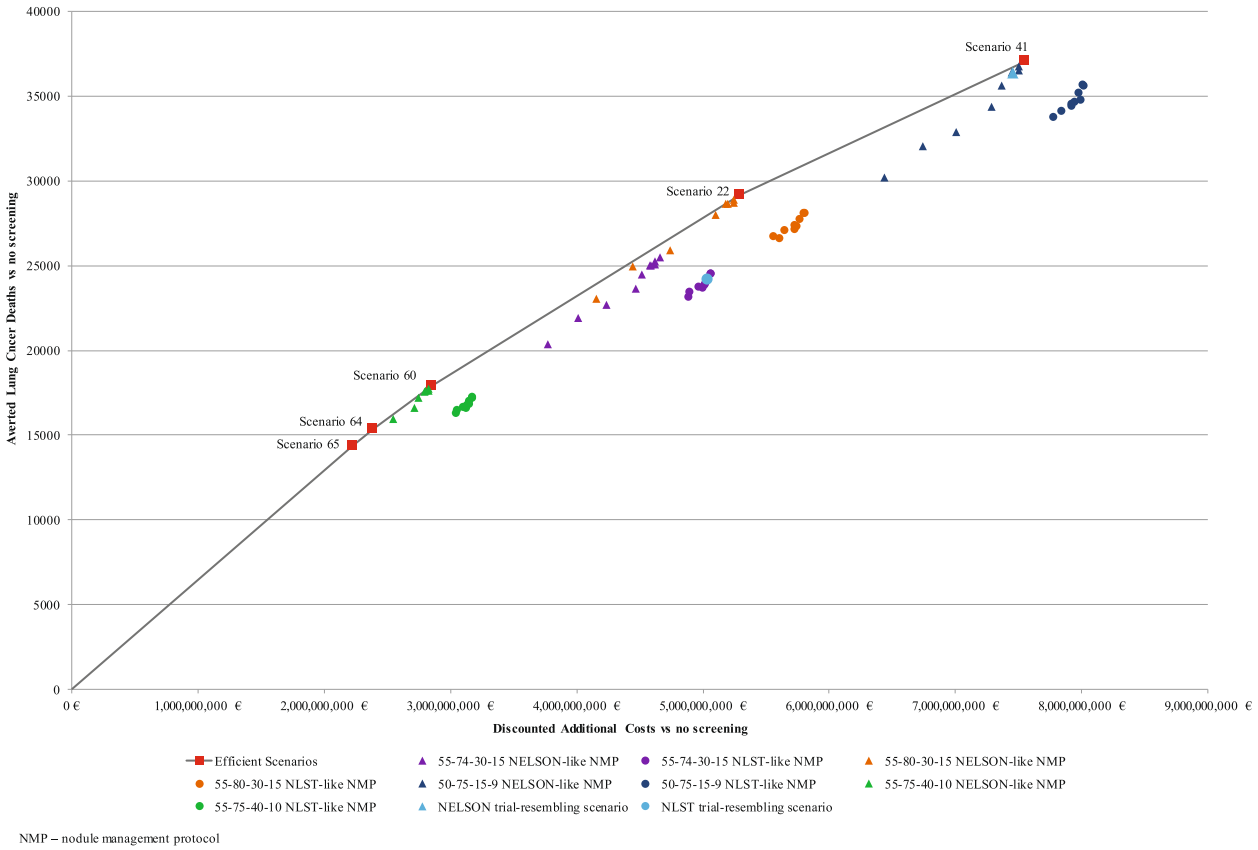

Fig. 6 The cost-effectiveness (cost per averted lung cancer death) of all evaluated scenarios and the scenarios that constitute an efficient frontier. The figure illustrates five scenarios judged to be efficient based on the cost per averted lung cancer death ratio. These scenarios constitute the efficient frontier. The other 71 evaluated scenarios are illustrated according to the population selection criteria and applied nodule management protocol (*NMP*). The figure illustrates the four evaluated eligibility criteria in different colours: 55-75-40-10 is given in *green*, 55-74-30-15 is given in *violet*, 55-80-30-15 is given in *orange* and 50-75-15-9 is given in *dark blue*. The scenarios which apply the NLST-like nodule management are illustrated with a *circular shape*. The scenarios which apply the NELSON-like nodule management are illustrated with a *triangular shape*. The figure does not specify in colour or a shape the evaluated variations of the threshold values for the tumour size and growth in the NELSON-like and NLST-like scenarios. The scenarios which resemble the eligibility criteria and nodule management protocols of the NLST and NELSON clinical trials are illustrated in *light blue*. Descriptions of the scenarios are given in Table 1. Main outcomes and cost-effectiveness of the 76 baseline screening scenarios are given in Additional file 1: Table S12

ACER. Compared with perfect adherence (100%), decreasing adherence to 85% for the years following the initial screening led to a modest decline of ACER (around 1%). Screening strategy 60 (55-75-40-10-NELSON-VDT400-V300) becomes inefficient in the scenarios of the decreased adherence, decreased cost per CT exam and increased treatment cost (i.e. innovative treatment scenario). Due to high rates of detection and overdiagnosis, factors that increase ratio of treatment relative to the costs of screening have adverse effects on ICER compared to the previous efficient scenario. Scenario 65 (55-75-40-10-NELSON-VDT300-only) in turn becomes inefficient under conditions of increased screening costs. Expanding the period of the screening to 10 years did not considerably influence the cost-effectiveness. Detailed results of baseline and sensitivity analyses are available in Additional file 1: Sections 2.2–2.4.

Discussion

The microsimulation analysis shows that lung cancer screening of the high-risk population in Germany can be cost-effective. A program with less restrictive eligibility criteria would be more effective but would induce a higher ICER due to screening of people with a lower risk of lung cancer development. The selection of heavier smokers and limitation of the screened population yields the lowest cost-effectiveness ratio compared with the no screening scenario. Increasing the stopping age, i.e. following the recommendations of the USPSTF [2], prevents additional deaths from lung cancer but also leads to considerable additional costs and increased overdiagnosis. Overall, if decision-making is based on the results of estimation of efficiency of an intervention, the scenarios that constitute an efficient frontier should be considered for implementation because other scenarios are proven to be

Table 2 Main outcomes of the efficient scenarios

Scenario	Scenario characteristics[a]	Detected cancers at an early stage (I/II), %	Reduction in lung cancer mortality, %	Lung cancer deaths averted	Discounted life years gained	Interval cancer cases	Overdiagnosed cases	Overdiagnosis, %	Discounted total cost, million euro	Discounted additional costs vs no screening, million euro	Cost per life years gained vs no screening (uniform discounting), euro	Discounted cost per lung cancer death averted vs no screening, euro	ICER vs the previous efficient scenario, euro
Efficient scenarios based on the cost per life year gained ratio													
Scenario 65	55-75-40-10-NELSON-VDT300-none	67.31	9.95	14,373	133,222	23,057	6733	9.48	10,892	2232	16,754	155,287	16,754
Scenario 60	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	9.69	11,516	2855	17,321	159,625	19,707
Scenario 41	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	29,456	7556	20,870	203,792	23,804
Efficient scenarios based on the cost per averted lung cancer death ratio													
Scenario 65	55-75-40-10-NELSON-VDT300-none	67.31	9.95	14,373	133,222	23,057	6733	9.48	10,892	2232	16,754	155,287	155,287
Scenario 64	55-75-40-10-NELSON-VDT400-none	67.95	10.65	15,395	140,490	21,367	9184	11.73	11,057	2397	17,059	155,675	161,124
Scenario 60	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	19.69	11,516	2855	17,321	159,625	184,009
Scenario 22	55-80-30-15-NELSON-VDT400-V300	70.95	12.80	29,165	260,807	32,071	33,473	21.76	18,846	5296	20,307	181,597	216,454
Scenario 41	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	29,456	7556	20,870	203,792	285,630

[a]Scenarios are named ranging these values as follows: "population selection criteria-nodule management protocol-threshold values for growth rate and nodule size"

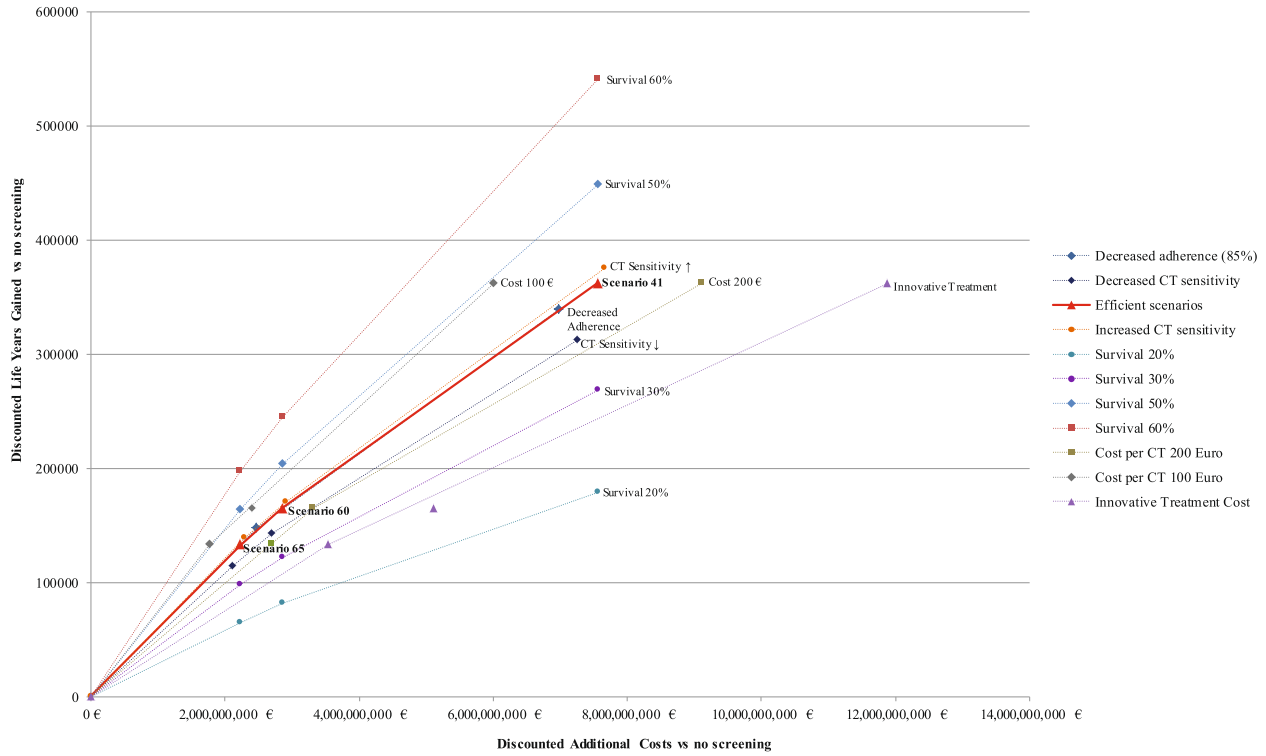

Fig. 7 The cost-effectiveness of the efficient scenarios (cost/LYG) in the sensitivity analyses. Scenario 60 is not efficient under conditions of decreased adherence, innovative treatment and cost per CT exam of 100 euro. Scenario 65 is not efficient when cost per CT exam is 200 euro

less efficient. The efficiency frontier itself is shaped by the applied measure of efficiency.

Our study provides two efficiency frontiers based on weighting two major benefits of screening (LYG and averted lung cancer deaths) against the resulting costs (additional costs relative to the no screening scenario). The comparative modelling study by de Koning et al. for the USPSTF [2] in turn used "screenings per lung cancer death averted" as a measure of the efficiency. Based on this measure, the authors concluded that the eligibility criteria 55-80-30-15 are more efficient than the original NLST criteria. Considering their results for the screenings per LYG as the efficiency measure, the 55-80-30-15 scenario is still more effective but less efficient than the 55-75-30-15 scenario. Although we applied the additional cost in the numerator of the cost-effectiveness ratio, our findings are consistent with those by de Koning et al.: the selection criteria 55-80-30-15 are more efficient than 55-74-30-15 if the efficiency is estimated using the cost per averted lung cancer death ratio but less efficient based on the cost per life year gained ratio. Overall, both efficient frontiers outlined in our study do not include scenarios with the 55-74-30-15 population selection criteria.

Additionally, the efficiency measure "screenings per lung cancer death averted" used by the USPSTF to give the recommendation for screening does not include the harms of overdiagnosis. In our study, the cost side of the cost-effectiveness ratio includes the costs (related to screening and treatment) of the overdiagnosed cases and by that the overdiagnosis is incorporated into the measure of efficiency. In screening for lung cancer, overdiagnosis is thought to be "the most extreme form of length-time bias" [30]. These cases include patients with tumours that would never have caused symptoms or been diagnosed in clinical settings. Stopping screening at age 80 leads to substantially higher numbers of overdiagnosed cases. This also has been shown in the studies by ten Haaf et al. [18] and de Koning et al. [2]. In our analysis, the costs of the overdiagnosed cases account for about 30% of the difference in costs between the 55-80-30-15 and 55-74-30-15 scenarios. If the impact of overdiagnosis on the quality of life was included into estimation of the efficiency, it would be expected to further reduce the effectiveness and efficiency of the screening of an older population.

Ideally, all benefits and harms which are considered to be relevant for the identification of an optimal screening strategy should be included into the measure of effectiveness and efficiency. However, this would require a defined efficiency threshold [31] or prioritisation and weighting of the benefits and harms made by decision-makers. The aim of our study was to evaluate strategies for an introduction

of a large-scale lung screening in Germany and to outline and discuss efficient scenarios rather than provide a solid recommendation.

Patient management strategy has a strong influence on long-term performance and cost-effectiveness of lung screening. The NELSON- and NLST-like nodule management protocols are comparably effective in reducing lung cancer mortality; however, the NELSON-like strategy is more successful in detection of early-stage lung cancers, yields fewer follow-up exams, and saves costs, and therefore may be preferable in clinical practice. The efficient screening scenarios highlight the combinations of the eligibility criteria and NELSON-like nodule management protocols, which may yield additional benefits without increasing the ICER. The cut-off volume for immediate diagnostic evaluation is a key element of the nodule management strategy. In the NELSON trial, the cut-off volume was defined as 500 mm^3 and higher. Our results show that a decrease to 300 mm^3 would be a more cost-effective strategy and may be justified for clinical practice. From the health economics perspective, our findings support previous inferences made by Horeweg and colleagues, who assessed probabilities of cancer development based on the NELSON data and concluded that patients with a screen-detected nodule of volume of 300 mm^3 or more should undergo immediate diagnostic work-up [20]. Additionally, variations of the nodule management elements show that the assessment of VDT at follow-up becomes more important if the threshold nodule volume is less restrictive (more than 500 mm^3).

It is important to note that a decreased cut-off volume may lead to an increased number of overdiagnosed cases. In our analysis, the majority of the overdiagnosed cases were patients with slowly growing adenocarcinomas and AIS. Due to their slow growth, these are rarely symptomatically diagnosed [32] but may be detected by screening. Our results also suggest that scenarios which exclude the threshold nodule volume as the indicator for immediate diagnostic evaluation and apply the assessment of VDT (at the follow-up exam 3 months later) as a sole malignancy predictor can considerably reduce overdiagnosis; however, this can come at a high price of missing LYG and averted lung cancer deaths. Although a number of cases and the costs of overdiagnosis can be calculated in model settings, their effects on the health outcomes and quality of life need to be further investigated and quantified.

In this study, the effect of screening on quality of life could not be included in the analysis due to lack of German data on values of quality-adjusted life years (QALYs) across the lung cancer stages, sexes and age groups. The cost-effectiveness ratios in terms of costs per QALY gained would be expected to be notably higher than the estimated cost/LYG ratios [7]. As long as the screening shifts the major part of diagnoses towards the early-stage cancers, more patients are likely to receive a resection operation. These patients are reported to have a considerably impaired quality of life during the first 2 years after lung resection but it may improve later [33, 34]. Additionally, with the application of QALYs, the negative effects of overdiagnosis and false positives would considerably increase [35, 36].

Several limitations are worth noting. Tumour growth is simulated using a Gompertzian growth model which does not capture abrupt changes in the development (growth) of the tumour. However, other studies have shown that cancer tumour growth can be well approximated by a Gompertz function [37]. Our approach to modelling of false positives is rather simplified and does not allow for a comprehensive analysis of the false-positive outcomes at screening. The question of how to decrease the number of false-positive cases remains unanswered and requires additional information, which clinical trials may provide in the future. The limitations form a direction for further research into lung screening in Germany. There is a need to collect detailed data on tumours at time of diagnosis about their size, stage, smoking habits of the patients, treatment costs and quality of life of German patients with lung cancer, along with factors affecting screening uptake among the target groups. The cost-effectiveness of a combination of a smoking cessation intervention with a screening program is worth investigating.

Despite the limitations, the present study contributes insights on the impacts of the nodule management protocol on the effectiveness and cost-effectiveness of the introduction of a large-scale lung screening program. Additionally, this work is the first modelling study of microsimulation design which examines cost-effectiveness of the introduction of a large-scale lung screening program in a European country. The presented findings are comparable to the results reported in NLST [38] and previous modelling studies [2, 14, 18]. Because the developed model contains very little input obtained from the NLST data, comparison with the outcomes of NLST may serve as validation of the model. Outcomes of the model for the scenario most similar to NLST (Additional file 1: Section 2.2, Table S10) show a resembling distribution of histologic classes and stages of lung cancers detected at screening and interval cancers [1]. NLST reports lung cancer mortality outcomes relative to radiography for a median follow-up of 6.5 years [38]. We could compare these with the outcomes of our microsimulation model for 7 years of follow-up (Additional file 1: Table S14). In our analysis lung cancer mortality is considerably higher in the no screening settings and in the NLST-resembling scenario than reported in the trial; however, the differences between mortality rates in the screening and no screening scenarios are close to the differences in mortality rates

between LDCT screening and radiography observed in NLST. Considering lung cancer mortality reduction as a ratio, due to the higher mortality rates the model reports a lower percentage (around 16%) in comparison to NLST (21%) [38]. However, it still falls into the range given by confidence interval calculations in NLST. Our model also predicts a higher all-cause mortality rate than observed in NLST. The higher mortality may be caused by an older population and a larger proportion of current smokers in the screened cohorts; additionally, the settings of a clinical study and a possible "healthy-volunteer" effect [38] may positively affect the mortality outcomes of the clinical trial.

Overall, reduction in lung cancer mortality calculated over a lifetime course ranges from 9.7 to 12.8% and stays similar to the values reported in previous studies [2, 18]. Furthermore, the difference in the mortality rates between the no screening and screening arms is the basis for the economic evaluation, and it is very similar to that of the NLST trial. We therefore suggest that application of survival data other than that reported in NLST has a limited influence on the presented findings.

The cost-effectiveness has been analysed in modelling studies in the USA [14] and Canada [18]. Due to the application of QALYs in the study by McMahon et al. (USA), the obtained cost-effectiveness ratios cannot be compared. Comparing the findings to the study by the Canadian team, the cost-effectiveness ratios obtained in this study lie within the range given by ten Haaf et al., despite differences in the applied cost inputs [18].

Overall, applicability of the presented results for other countries depends on the similarity of the cost structure and heavy smoker prevalence between the countries. The sensitivity analyses show that cost-effectiveness ratio is driven by cost per CT exam and other screening-related costs. The cost per CT exam taken in our study is not Germany-specific and is varied in the sensitivity analyses, giving an opportunity to transfer the results to other countries. The costs of lung cancer treatment tend to be higher in Germany, as in other European countries [39]. Pharmaceutical companies continue to keep prices higher in Germany based on the expectation that German prices will become reference prices for the pharmaceuticals in other European countries [40]. Lower costs of screening and lung cancer treatment in other countries may decrease the cost-effectiveness ratio and make population-based lung screening more cost-effective.

Due to differences in exposure to smoking in populations, cost structures and approaches to lung cancer treatment, efficient scenarios of lung screening can vary between the European countries. However, the main findings on the impacts of the nodule management protocol and population selection criteria on the cost-effectiveness of the screening can be applied to other countries.

Conclusions

This study quantifies the effect of nodule management approaches on the benefits, harms and cost-effectiveness of lung screening. Our analysis shows that the nodule management protocol has a considerable effect on screening performance and should be considered in greater detail when defining optimal screening strategies. It is the first cost-effectiveness analysis of lung cancer screening using a microsimulation design performed in a population-based setting in Germany. These results can support decision-making processes in lung cancer prevention and direct creation of guidelines for LDCT lung cancer screening to benefit the German population.

Additional file

Additional file 1: Microsimulation model components, modelling methods, input parameters and additional summaries of results. (PDF 3708 kb)

Abbreviations

ACER: Average cost-effectiveness ratio; AIS: Adenocarcinoma in situ; ICER: Incremental cost-effectiveness ratio; LDCT: Low-dose computed tomography; LYG: Life years gained; NELSON: Netherlands-Leuvens Screening Trial; NLST: National Lung Screening Trial; QALY: Quality-adjusted life year; USPSTF: US Preventive Services Task Force; VDT: Volume doubling time

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Availability of data and materials

The data used in the present analyses can be found in the studies cited in the text. The resulting data is also presented in Additional file 1. All other datasets generated during the simulations are available from the corresponding author upon reasonable request.

Authors' contributions

MT and AK designed the study and developed the microsimulation model. MT constructed the population, screening and life history modules of the microsimulation model and performed the main and sensitivity analyses. AK constructed the natural history, clinical detection and survival modules of the microsimulation model and performed the model calibration. IA gathered relevant input parameters, calculated lifetime treatment costs and included them in the cost-effectiveness analyses. Authors MT, AK and IA participated in drafting the manuscript and the additional file materials. Medical experts TW, JV-C and HG revised the manuscript critically and provided important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Outside the submitted work during conduction of the study, T Welte has received grants from the Ministry of Research and Education and personal fees from AstraZeneca, GlaxoSmithKline, Bayer, Novartis, Pfizer, Boehringer and Merck Sharp & Dohme. M Treskova, I Aumann, H Golpon, J Vogel-Claussen and A Kuhlmann have declared no conflicts of interest.

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References

1. The National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368:1980–91. doi:10.1056/NEJMoa1209120.
2. de Koning HJ, Meza R, Plevritis SK, ten Haaf K, Munshi VN, Jeon J, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med. 2014;160:311–20. doi:10.7326/M13-2316.
3. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer. Chest. 2013;143:e78S–92. doi:10.1378/chest.12-2350.
4. Humphrey LL. Screening for lung cancer with low-dose computed tomography: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2013;159:411. doi:10.7326/0003-4819-159-6-201309170-00690.
5. Moyer VA, on behalf of the U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:330–8.
6. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers J-WJ, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol. 2014;15:1342–50. doi:10.1016/S1470-2045(14)70387-0.
7. van der Aalst CM, ten Haaf K, de Koning HJ. Lung cancer screening: latest developments and unanswered questions. Lancet Respir Med. 2016;4:749–61. doi:10.1016/S2213-2600(16)30200-4.
8. Pastorino U. Lung cancer screening. Br J Cancer. 2010;102:1681–6. doi:10.1038/sj.bjc.6605660.
9. Kauczor H-U, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, et al. ESR/ERS white paper on lung cancer screening. Eur Radiol. 2015;25:2519–31. doi:10.1007/s00330-015-3697-0.
10. Tammemagi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. N Engl J Med. 2013;368:728–36. doi:10.1056/NEJMoa1211776.
11. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers. JAMA. 2003;289:313. doi:10.1001/jama.289.3.313.
12. Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. Lung Cancer. 2005;48:171–85. doi:10.1016/j.lungcan.2004.11.001.
13. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. Lung Cancer. 2001;32:227–36.
14. McMahon PM, Kong CY, Bouzan C, Weinstein MC, Cipriano LE, Tramontano AC, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. J Thorac Oncol. 2011;6:1841–8. doi:10.1097/JTO.0b013e31822e59b3.
15. Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. Health Aff. 2012;31:770–9. doi:10.1377/hlthaff.2011.0814.
16. Shmueli A, Fraifeld S, Peretz T, Gutfeld O, Gips M, Sosna J, Shaham D. Cost-effectiveness of baseline low-dose computed tomography screening for lung cancer: the Israeli experience. Value Health. 2013;16:922–31. doi:10.1016/j.jval.2013.05.007.
17. Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. Chest. 2003;124:614–21. doi:10.1378/chest.124.2.614.
18. ten Haaf K, Tammemägi MC, Bondy SJ, van der Aalst CM, Gu S, McGregor SE, et al. Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: a microsimulation modeling analysis in Ontario, Canada. PLoS Med. 2017;14, e1002225. doi:10.1371/journal.pmed.1002225.
19. Ruano-Ravina A, Pérez-Ríos M. Lung cancer screening with low-dose CT: more questions than answers. Lancet Oncol. 2015;16:e3–4. doi:10.1016/S1470-2045(14)71157-X.
20. Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol. 2014;15:1332–41. doi:10.1016/S1470-2045(14)70389-4.
21. Lange C, Jentsch F, Allen J, Hoebel J, Kratz AL, von der Lippe E, et al. Data resource profile: German Health Update (GEDA)—the health interview survey for adults in Germany. Int J Epidemiol. 2015;44:442–50. doi:10.1093/ije/dyv067.
22. Statistisches Bundesamt. Bevölkerung und Erwerbstätigkeit: Ausgangsdaten der Bevölkerungsfortschreibung aus dem Zensus 2011. Wiesbaden: Federal Statistical Office; 2015.
23. Moolgavkar SH, Luebeck G. Two-event model for carcinogenesis: biological, mathematical, and statistical considerations. Risk Anal. 1990;10:323–41. doi:10.1111/j.1539-6924.1990.tb01053.x.
24. McMahon PM, Kong CY, Johnson BE, Weinstein MC, Weeks JC, Tramontano AC, et al. Chapter 9: the MGH-HMS lung cancer policy model: tobacco control versus screening. Risk Anal. 2012;32:S117–24. doi:10.1111/j.1539-6924.2011.01652.x.
25. Erasmus University Medical Center. MISCAN-Lung (Erasmus) MIcrosimulation SCreening Analysis (MISCAN) lung model. CISNET_ModelProfile_LUNG_ERASMUS_001_01132012_83607.pdf. Accessed 28 Jul 2016.
26. Horeweg N, van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. Eur Respir J. 2013;42:1659–67. doi:10.1183/09031936.00197712.
27. Department of Health. The likely impact of earlier diagnosis of cancer on costs and benefits to the NHS. London: Department of Health; 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213788/dh_123576.pdf. Accessed 17 Aug 2016.
28. Schremser K, Rogowski WH, Adler-Reichel S, Tufman ALH, Huber RM, Stollenwerk B. Cost-effectiveness of an individualized first-line treatment strategy offering erlotinib based on EGFR mutation testing in advanced lung adenocarcinoma patients in Germany. Pharmacoeconomics. 2015;33:1215–28. doi:10.1007/s40273-015-0305-8.
29. Callister MEJ, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax. 2015;70 Suppl 2:ii1–54. doi:10.1136/thoraxjnl-2015-207168.
30. Postmus PE. Screening for lung cancer, an ongoing debate. Ann Oncol. 2008;19 Suppl 7:vii25–7. doi:10.1093/annonc/mdn464.
31. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics. 2008;26:733–44.
32. Read WL, Page NC, Tierney RM, Piccirillo JF, Govindan R. The epidemiology of bronchioloalveolar carcinoma over the past two decades: analysis of the SEER database. Lung Cancer. 2004;45:137–42. doi:10.1016/j.lungcan.2004.01.019.
33. Schulte T, Schniewind B, Dohrmann P, Kuchler T, Kurdow R. The extent of lung parenchyma resection significantly impacts long-term quality of life in patients with non-small cell lung cancer. Chest. 2009;135:322–9. doi:10.1378/chest.08-1114.
34. Schulte T, Schniewind B, Walter J, Dohrmann P, Kuchler T, Kurdow R. Age-related impairment of quality of life after lung resection for non-small cell lung cancer. Lung Cancer. 2010;68:115–20. doi:10.1016/j.lungcan.2009.05.019.
35. Wiener RS, Gould MK, Woloshin S, Schwartz LM, Clark JA. What do you mean, a spot? A qualitative analysis of patients' reactions to discussions with their physicians about pulmonary nodules. Chest. 2013;143:672–7. doi:10.1378/chest.12-1095.
36. van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, Scholten ET, van Klaveren RJ, de Koning HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J. 2011;38:154–61. doi:10.1183/09031936.00123410.
37. Detterbeck FC, Gibson CJ. Turning gray: the natural history of lung cancer over time. J Thorac Oncol. 2008;3:781–92. doi:10.1097/JTO.0b013e31817c9230.
38. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409. doi:10.1056/NEJMoa1102873.

39. McGuire A, Martin M, Lenz C, Sollano JA. Treatment cost of non-small cell lung cancer in three European countries: comparisons across France, Germany, and England using administrative databases. J Med Econ. 2015;18: 525–32. doi:10.3111/13696998.2015.1032974.
40. Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, Leufkens H. Impact of external price referencing on medicine prices — a price comparison among 14 European countries. Southern Med Review. 2012;5:34–41.

Additional file 1

The first section of the current document contains a detailed description of the developed microsimulation model. The second part gives main results of model calibration and simulation.

Content

Tables

Figures

1. Methods

1.1. Modules of the microsimulation model

The model is of modular design and comprises of the following structural modules: Population, Natural History, Clinical Detection and Survival, Screening and Life History.

1.1.1. Population module

Population module creates a screening population with the given demographic structure and smoking patterns. The individuals in the simulated population were characterized by gender, age at model entry point and then defined by the age at the point of initial smoking, age at smoking cessation and the average number of cigarettes consumed per day. Smoking history determines the exposure to cigarette smoke (first hand), which along with age and gender governs age of death from other causes.

Smoking behaviour data were obtained from two national health surveys conducted between 2008 and 2012: the German Health Interview and Examination Survey for Adults (DEGS) and the German Health Update (GEDA)[1]. Due to the data availability, the demographic structure was taken from the year of 2012[2]. Based on the smoking behaviour data and demographic structure, the population for the simulation was obtained via bootstrapping 10% of the German population. Smoking behaviours of current smokers were extrapolated over the course of a lifetime and during the modelled years the current smokers could quit smoking. The smoking cessation age was calculated by using the smoking cessation probabilities, which were assigned according to estimates obtained based on the data from the national health surveys.

1.1.1.1. Other-cause mortality

In the Population module an individual age of death from other causes than lung cancer is simulated based on age at entry the model, gender and the smoking status: never-, current- or former smoker. Five-year survival probabilities across age, gender and the smoking status were constructed based on the estimates obtained by Woloshin et al[3] and extrapolated using the recent life tables for the German population[2]. Other-cause mortality was introduced into the model as a competing risk and computed by applying the probability estimates and two random numbers (for each individual) which defined a five-year age interval in which the person may die from other causes and then the exact age of death within this interval.

1.1.2. Natural History module

The Natural History module simulates the development of lung cancer during individual life course. The sequence of events starts with onset of the first malignant cell, evolves through the progressive stages of lung cancer and ends with the death from the cancer.

The onset of the first malignant cell is simulated by using the biological two-stage clonal expansion (TSCE) model described by Moolgavkar and Luebeck[4], where age, gender and personal exposure to cigarette smoke are translated into the piecewise constant parameters of the hazard functions. Onset lung cancer is modelled as a competing risk between four histological types: small cell-, large cell-, squamous cell- and adenocarcinomas. For

each histological type, we drew an individual age at onset of carcinogenesis from a respective survival function. The histologic type that develops first is defined as the active cancer. We assume that 20% of adenocarcinomas are of type adenocarcinoma in situ[5]. Additionally, if the onset of cancer takes place, we assume a single malignant nodule per person.

The progression of the cancer is characterised by its growth, nodal involvement and occurrence of distant metastases. Threshold values of tumour volumes at the stages of nodal involvement and distant metastases depend on the histologic cancer type and are randomly drawn from log-Normal distributions. We applied a Gompertz function to model tumour growth over time[5]. This function determines the individual age at every stage of disease progression given the respective threshold volumes are reached (see section Modelling details of the Natural History, Clinical detection and Survival modules).

1.1.3. Clinical detection and Survival module

Clinical detection and Survival module simulates symptomatic detection of lung cancer, which includes age and tumour volume at the time of diagnosis, and age of death from lung cancer. The distribution of the tumour volumes at time of diagnosis is given by the log-Normal distribution; age at the time of diagnosis is analogously calculated by using the tumour growth function. Persons with clinical detection undergo diagnostic procedures which include PET CT, EBUS bronchoscopy and head MRI [6]. The diagnosis is assigned according to the TNM Classification of Malignant Tumours (TNM) by the Union for International Cancer Control (UICC). Treatment is not explicitly modelled, however, its effects are implicitly included in lung cancer survival function. The survival depends on the histological class and stage at the time of diagnosis and follows the Weibull distribution[7] (see Table 1). It is assumed that death from lung cancer occurs after the time of clinical diagnosis.

Table S1: Parameters for the long-term survival probability and the Weibull distributions for time period from clinical diagnosis to lung cancer death by cell type and stage at diagnosis [7].

Histological class	Stage at Diagnosis	Long-term survival probability	Weibull distributions	
			Mean	Shape
Squamous cell- carcinoma	I , II	0.180	2.419	0.573
Squamous cell-carcinoma	III , IV	0.060	0.752	0.641
Adeno- and Large cell-carcinoma	I , II	0.290	4.783	0.676
Adeno- and Large cell-carcinoma	III , IV	0.050	0.674	0.607
Small cell-carcinoma	I , II	0.080	1.049	0.727
Small cell-carcinoma	III , IV	0.010	0.507	0.738

1.1.4. Modelling details of the Natural History, Clinical detection and Survival modules

1.1.4.1. Onset of the first malignant cell:

Onset of the first malignant cell of each histological class is expressed by the biological two-stage clonal expansion (TSCE) model. The hazard rates and the survival probabilities are given by the equations below which were adopted from an R package "MIcrosimulation Lung Cancer (MILC) model" by Chrysanthopoulou AS. [8]

Hazard function for the development of the first malignant cell is described by [8]:

$$h(t) = \frac{\upsilon\mu X\,(e^{(\gamma+2B)t} - 1)}{\gamma + B\,(e^{(\gamma+2B)t} + 1)}$$

where X is total number of normal cells, υ is the normal cell initiation rate, μ is the malignant transformation rate, γ and B are piecewise constant parameters which are determined by:

$$\gamma = \alpha - \beta - \mu \text{ and } B = \frac{1}{2}\,(-\gamma + \sqrt{\gamma^2 + 4\alpha\mu})$$

where α the cell division rate and β is the rate of programmed cell death.

For the hazard function, a cumulative hazard function than is constructed and given by [8]:

$$H(t) = \frac{\nu\mu X}{\gamma + B} * \left(- t + \frac{1}{B} * \log(\gamma + B + B * e^{(\gamma+2B)t})\right)$$

with

$\alpha = \alpha_0\,(1 + \alpha_1 q(t)^{\alpha_2})$ and $\gamma = \gamma_0\,(1 + \alpha_1 q(t)^{\alpha_2})$,

where $q(t)$ is the average number of cigarettes consumed per day at age *t* and α_0 and γ_0 represent coefficients for never smokers. The parameters are given in Table 2.

Table S2: Parameters for the cumulative hazard functions

Parameter	Males	Females	Reference
Total number of normal cells (X)	10^7	10^7	[9] see Table 2 for CPS-II cohort.
Division rate of initiated cells non-smokers(α_0) smokers: α_1 ; α_2	 7.7 0.6 ; 0.22	 15.82 0.5 ; 0.32	
Piecewise constant parameters non-smokers (γ_0)	0.09	0.071	
The normal cell initiation rate non-smokers (ν_0)	$= \mu$	$= \mu$	
The normal cell initiation rate smokers (ν_1)	0	0.02	

For each histological class, the cumulative hazard functions are transformed into the survival functions which describe the time of the onset of lung cancer and are given by [8]:

$$S(t) = \exp\{-H(t)\} = \exp\left\{-\int_0^t h(x)\,dx\right\}$$

For each individual with onset carcinogenesis, the ages of onset of the first malignant cell of each histological type are drawn from the respective survival functions. The type of the active cancer and age of onset of carcinogenesis are modelled through competing risks between the four histological types and are determined by the histological type of the earliest cancer.

The life course is segmented into periods which are defined by age, gender and smoking status. Table 3 describes the division. The periods are bounded by age given by *a* and *b*, $0 < a < b < t_d$, where t_d depicts the age of death. Over these periods the survival functions are differently parameterized to express differences in the risk of onset of carcinogenesis. The parameters for the survival functions are given in Table 4 and are constant over the given period.

Table S3: Age boundaries ("a and b") for parametrization of age-dependent risk of the onset of the first malignant given in years by gender and histological class.

	Small cell-carcinoma	Large cell-carcinoma	Squamous cell-carcinoma	Adeno/AIS*-carcinoma
Male				
Age1 (a)	50.88	50.31	49.75	50.41
Age2 (b)	64.54	66.09	62.62	66.37
Female				
Age1 (a)	56.88	56.61	57.05	56.07
Age2 (b)	79.46	79.28	79.89	79.19

* adenocarcinoma *in situ*

Table S4: Parameters for malignant conversion rate of initiated cells (μ)* by gender, period and cell type.

	Small cell-carcinoma	Large cell-carcinoma	Squamous cell-carcinoma	Adeno/AIS-carcinoma
Male				
0 - a	2.13E-08	1.12E-08	2.70E-08	5.64E-08
a - b	2.67E-08	1.05E-08	4.14E-08	8.58E-08
b - 100	5.84E-08	2.07E-08	9.90E-08	1.26E-07
Female				
0 - a	4.51E-08	2.00E-08	3.96E-08	1.27E-07
a - b	7.37E-08	2.08E-08	7.46E-08	1.70E-07
b - 100	5.26E-08	1.71E-08	5.91E-08	4.60E-08

* The parameters were fitted using data on lung cancer incidence by Eberle 2015 and the German cancer registry [10,11].

Depending on the smoking status an individual life course can be divided into periods as follows. The periods are denoted by T_1, T_2, T_3 and T_4.

Never smoker:

For never smokers a life course is divided into three periods in which the survival function is parametrized with different malignant conversion rates (Table 4).

$$S(t) = \exp\left\{ - \int_0^{T_1} h(x)\, dx - \int_{T_1}^{T_2} h(x)\, dx - \int_{T_2}^{t_d} h(x)\, dx \right\},$$

with $T_1 = a$ and $T_1 = b$

Current smoker:

For current smokers a life course is divided into four periods which are defined by the age boundaries (as for never smokers) and age at start smoking. The age at smoking initiation can fall into any of the three periods and alter the parameterization for the hazard and survival functions over the periods following the time at smoking initiation as follows:

$$S(t) = \exp\left\{ - \int_0^{T_1} h(x)\, dx - \int_{T_1}^{T_2} h(x)\, dx - \int_{T_2}^{T_3} h(x)\, dx - \int_{T_3}^{t_d} h(x)\, dx \right\},$$

with T_{st} is age at start smoking, $0 < a < b < t; 0 < T_{st} < t_d$, and:

$$T_1 = \begin{cases} T_{st}, & T_{st} \le a \\ a, & T_{st} > a \end{cases}$$

$$T_2 = \begin{cases} a, & T_{st} \le a \\ T_{st}, & a < T_{st} < b \\ b, & T_{st} \ge b \end{cases}$$

$$T_3 = \begin{cases} T_{st}, & T_{st} \ge b \\ b, & T_{st} < b \end{cases}$$

Former smoker:

For former smokers a life course is divided into five periods given by the age boundaries (as for non-smokers), age at smoking initiation and age at smoking cessation. The hazard and survival functions are respectively parameterized over the pre-smoking, smoking and post-smoking periods.

The survival functions for former smokers are described as follows:

$$S(t) = \exp\left\{- \int_0^{T_1} h(x)\,dx - \int_{T_1}^{T_2} h(x)\,dx - \int_{T_2}^{T_3} h(x)\,dx - \int_{T_3}^{T_4} h(x)\,dx - \int_{T_4}^{t_d} h(x)\,dx\right\},$$

with T_{st} age at initial cigarette smoking and T_q age of cessation, $0 < a < b < t_d; 0 < T_{st} < T_q < t_d$,

and:

$$T_1 = \begin{cases} T_{st}, & T_{st} \le a \\ a, & T_{st} > a \end{cases}$$

$$T_2 = \begin{cases} T_q, & T_q < a \\ a, & T_{st} < a \text{ and } T_q \ge a \\ T_{st}, & a < T_{st} < b \end{cases}$$

$$T_3 = \begin{cases} a, & T_q \ge a \\ b, & T_{st} < b \text{ and } T_q \ge b \\ T_q, & T_{st} < b \text{ and } T_q < b \\ T_{st}, & T_{st} \ge b \end{cases}$$

$$T_4 = \begin{cases} b, & T_q < a \\ T_q, & T_{st} \ge b \end{cases}$$

1.1.4.2. Tumour growth

The following Gompertz function for tumour growth is applied:

$$V(t) = V_0 \cdot e^{\frac{\beta}{\alpha}\cdot(1-e^{-\alpha\cdot t})}$$

Where V_0 and $V(t)$ represent initial tumour volume and $V(t)$ tumour volume at time t, α and β are the location and scale parameters of the Gompertz distribution.

Maximum tumour volume V_{max} in the Gompertz function is given by:

$$V_{max} = V_0 \cdot e^{\frac{\beta}{\alpha}}$$

With a given V_{max} , the volume of the tumour developed over time t is expressed by:

$$V(t) = V_{max} \cdot \left(\frac{V_0}{V_{max}}\right)^{e^{(-\alpha\cdot t)}}$$

and time needed to reach volume $V(t)$ can be computed as:

$$t = \frac{\ln\left(\log_{\frac{V_0}{V_{max}}} \frac{V(t)}{V_{max}}\right)}{-\alpha},$$

where α is the growth rate which is drawn from lognormal distributions parameterized according to the histological class (see Table 5) [5].

Relationship between V_{max} and a set diameter is described by:

$$V_{max} = \frac{\pi}{6}(D)^3$$

where D is a given diameter.

Limits of diameters for V_{max} are fixed to 277 mm for all histological types except adenocarcinoma *in situ* for which the limit of diameter for V_{max} is set to 30 mm.

Table S 5: Distribution of alpha parameters, α , for the growth rate applied in the Gompertz tumour growth function [5].

Histological class	Distribution of alpha parameter	Mean (SD) Diameter at 0.5cm	Mean (SD) Diameter at 1.0cm	Mean (SD) Diameter at 1.5cm
Adeno/AIS-carcinoma	logN(-7.765, 0.5504)	187(160)	227(194)	260(222)
Large cell-carcinoma	logN(-6.59942, 0.68862)	61(61)	74(74)	85(85)
Small cell-carcinoma	logN(-5.44357, 0.611485)	19(16)	23(20)	26(23)
Squamous cell-carcinoma	logN(-6.6111, 0.7935)	65(72)	79(87)	90(100)

1.1.4.3. Modelling regional and distant stages of the disease progression

The disease progression is featured via tumour growth, nodal involvement (regional stage) and metastases (distant stage). It has been previously shown that with a Gompertzian tumour growth function, the disease progression through advanced stages over time are characterized by specific tumour volumes, location and presence of metastases can be well described by applying log-Normal distributions [8].

Threshold tumour volumes for regional and distant stages are drawn from log-Normal distributions constructed for each histological class i ($i = 1,2,3,4$) and stage j (j=regional, distant, clinical diagnosis) as $lognormal(\mu_{i,j}, \sigma_{i,j}^2)$. If a person's threshold volume exceeds computed for her V_{max}, the corresponding cancer stage will not be reached during the lifetime of this person.

The threshold volumes across the histological classes and progression stages are given in the Table 6 below. The log-Normal distributions are constructed by transforming these volumes to mean and standard deviations of the $lognormal(\mu_{i,j}, \sigma_{i,j}^2)$ distributions.

Table S6: Threshold values for volumes in mm^3 used to construct the log-Normal distributions in modelling of the disease progression. The parameters were fitted using data on lung cancer stages by Eberle 2015 [11]

Histological class	**Regional stage** Mean (SD)	**Distant stage** Mean (SD)	**Diagnosis before the regional stage** Mean (SD)	**Diagnosis after the regional stage** Mean (SD)
Small cell-carcinoma	610* (650)	4,710* (4,140)	4,787 (4,787)	9,031 (9,031)
Large cell-carcinoma	2,299 (2,299)	18,482 (18,482)	8,262 (8,262)	25,144 (25,144)
Squamous cell-carcinoma	8,466 (8,466)	74,610 (74,610)	24,458 (24,458)	56,418 (56,418)
Adeno/AIS-carcinoma	3,038 (3,038)	17,376 (17,376)	9,899 (9,899)	27,304 (27,304)

*adopted from McMahon et al 2012 [5]

1.1.5. Screening module

Screening module contains several structural components: eligibility assessment, screen-detection, nodule management (includes follow-up), diagnostic work-up and lung cancer survival.

1.1.5.1. Eligibility assessment

The eligibility criteria include qualifying age range, accumulated pack-years and number of years since cigarette cessation. Once eligible an individual undergoes a screen chest exam with LDCT.

1.1.5.2. Screen-detection

The probability of a screen-detection of a nodule depends on the presence of lung cancer and the sensitivity of the LDCT-test. The sensitivity of CT varies with nodule size and its location (Table 7). The location is considered of two types, central and peripheral, and varies with histological classes[5]. In the case of screen-detection of a nodule, the person proceeds through the nodule management algorithm. In the case of no detection, the person is scheduled for the next screening round.

1.1.5.3. Nodule management algorithms

The nodule management includes the nodule size assessment, classification of the screening test results and follow-up scans. The output of the nodule management predetermines whether the person goes through the work-up component or is scheduled for the next screening round. During simulation only one of the NLST and NELSON nodule management is switched depending on the screening scenario under evaluation.

See Figures 2 and 3 in the main text.

In the NELSON-line nodule management protocol, based on the assessed volume (V), the screening-detected nodule is classified as a negative ($V<V_{fup}$), positive ($V\geq V_{cut}$) or indeterminate result ($V_{fup} \leq V <V_{cut}$). Individuals with the negative initial results continue with annual screening. Individuals with the positive initial results undergo immediate diagnostic work-up. Persons with the indeterminate results undergo a follow-up imaging exam at three months after the initial screening. Results of the follow-up exam are determined by the nodule volume and the growth rate. The growth rate is defined by assessment of volume change (%) and volume

doubling time (VDT) [121]. At the follow-up the initial results are reclassified as positive if the nodule volume reaches or exceeds the cut-off volume (V_{cut}) and/or with VDT less than the threshold value (VDT_{cut}) defined by the scenario. The person with these results undergoes the work-up diagnostic procedures. If VDT is more than the threshold value, the person proceeds with the annual periodicity follow-up till the requirements for the positive result are met. Volumes at the follow-ups are compared with the volume of the initial screen-finding.

The NLST-like nodule management algorithm includes diametric assessment of the nodule size and a sequence of follow-up procedures where tumour growth is estimated as a change (%) in the nodule diameter relative to the result at the initial screening. Based on the assessed diameter (D) the nodule is placed into one of the three categories: negative ($D<D_{fup}$), positive intermediate ($D_{fup} \leq D < D_{cut}$) and positive ($D \geq D_{cut}$)[13]. People with negative initial results proceed to the next screening round. People with the positive initial results undergo diagnostic evaluation. Individuals with the intermediate initial results undergo a course of follow-up chest imaging exams with LDCT. The follow-up can occur with the fixed periodicity: at three, six and twelve months after the initial screening. The number of follow-up scans is managed according to the diameter of the nodule and its growth during the time between the initial screening and the follow-up exam. The growth is defined as a percentage increase in diameter and determined in screening scenario ($Growth_{cut}$). Measurement of growth is based on the comparison between the actual diameter and the diameter of the nodule found at the initial screen. In the follow-up course the diameter of 7 mm is the threshold diameter to undergo diagnostic evaluation. If at the first follow-up (at 3 months after the initial screening) no growth is detected, the person continues with an annual periodicity follow-up till the requirements for the positive result are met ($D \geq 7$ mm) [13]. If the growth is present, the diameter is assessed. In case the diameter does not exceed the threshold, the person undergoes the next follow-up round within 6 month after the initial screening with assessment of the diameter. If the diameter of the nodule at the second follow-up (6 months) is over 7 mm, the person proceeds with the diagnostic work-up. In case the nodule size does not reach the threshold the person continues with the annual periodicity follow-up till the requirements for the positive result are met ($D \geq 7$ mm). The cancer-indicating values for nodule size (V_{cut}, D_{cut}) and tumour growth ($VDT_{cut}, Growth_{cut}$) were taken from the trials and varied in the screening scenarios.

1.1.5.4. Diagnostic work-up

The diagnostic work-up component models a one-month long period when a patient undergoes a CT-supported biopsy to determine malignancy of the nodule and a head MRI (magnetic resonance imaging) and proceed with diagnosis. Screen-detected nodules are staged according to the TNM system based on the tumour diameter/volume and the progression state at time of diagnosis. During the diagnostic work-up a complication (pneumothorax) may occur, which is modelled as an age-dependent probability (see Table 7).

1.1.5.5. Lung cancer survival

Description is given in the main text.

[1] $VDT = \frac{\ln(2)\Delta t}{\ln(V_2)-\ln(V_1)}$,

where Δt is time in days between the initial screening and the follow-up exams, V_1 is the nodule volume at the time of initial screening, and V_2 is the volume at the follow-up

1.1.6. Life history module

For the screening and no screening scenarios, the *Life History* module calculates the final life scenario for each individual, providing the chronological sequence of events and final age of death along with the cause of death. The module also calculates events of false-positive cases, overdiagnosed cases, interval cancers and radiation induced cancer and deletes obsolete cases.

1.1.6.1. False-positive findings

False-positive findings of different sizes are simulated for people without lung cancer based on the outcomes of the clinical trials. For the NLST-based on nodule management algorithm, the number of follow-up scans and work-up of false-positive findings are estimated using the ratio of true positive to all positive findings obtained from the NLST trial results. For the NELSON nodule management follow-ups and work-ups of false-positive findings are estimated relative to the number of CT scans. The respective rates are calculated based on the results of the NELSON trial. Diagnostic work-up of false-positive finding includes a CT-supported biopsy, which may induce pneumothorax as a complication with the age-dependent probability (see Table 7). The false-positive findings are retroactively included into the model.

1.1.1.1. Overdiagnosed cases

A case of overdiagnosis is defined as an individual whose lung cancer is expected to be clinically diagnosed after her age of death from other causes but whose cancer is screen-detected before this age (de Koning, Harry J. et al. 2014).

1.1.1.2. Interval lung cancer

Interval lung cancer is defined as a cancer which is not initially screen-detected but is diagnosed in the time between scheduled screening exams [14]. The module incorporates two sources of interval lung cancer occurrence. The first is false-negative screening results, which can occur due to the nodule size-dependent sensitivity of CT scan. The second is the truly interval lung cancer, which develops and is diagnosed within the time interval between two screenings.

1.1.1.3. Radiation-induced cancer

Radiation-induced cancer death may occur in a 10–20-year period after the screening program. The risk is calculated as one radiation-induced cancer death per 2500 screened individuals who received 8 mSv in a 3-year period; these estimates are obtained based on the NLST trial [15].

1.1.7. Screening scenarios

Based on Table 1 in the main paper, name of a scenario contained specified population, nodule management protocol, thresholds for nodule size and nodule growth. The scenarios were additionally numbered from 1 to 76.

The scenarios that simulated NELSON-like and NLST-like nodule management protocols were 50-75-15-9-NELSON-VDT400-V500 and 55-74-30-15-NLST-GR10-D10.

1.1.8. Screening module: Parameters overview

Table S7: Parameters of the screening component

Parameter	NLST	NELSON	Reference
Sensitivity of screening CT exam for peripheral lesions. Sensitivities for a central lesion of the same diameter are 25% lower (Probability of detection)	0.63 for D≥1mm 0.77 for D≥4mm 1.00 for D≥8mm		[16]
Specificity of screening CT exam	0.98		
Threshold nodule size for follow-up	4mm ≤ D < 10mm	50 mm^3 ≤V<500 mm^3	
Rate of "Stage II" at diagnosis: parameter for a binomial function which randomly defines whether the person at regional stage* is diagnosed with "Stage II" at screening: at no screening:	 0.298701299 0.188034188		[13]
Complication rate at work up: malignant nodule: D≤2cm malignant nodule: 2<D≤4cm malignant nodule: D>4cm benign nodule	 0.33 0.3 0.15 0.23		[17]
Long-term survival probability for stages I and II in the case the patients would die from lung cancer in the no screening scenario	0.4		[7]

*people at regional stage of cancer progression can be diagnosed either with stage II or stage III of TNM system.

1.2. Model calibration

The calibration process was performed in two steps. Firstly, for each lung cancer type mean and standard deviation of the log-Normal distributed threshold volumes of lymph nodes involvement (regional), distant metastases (distant) and clinical diagnosis were simultaneously calibrated to fit the German UICC data on diseases stage at time of diagnosis [11]. The parameters for the log-Normal distribution of the tumour volumes at time of clinical diagnosis differed depending on the disease stage progression: before and after the lymph nodes involvement (regional stage). Table 6 (section 1.1.4.3) presents the applied parameters in the columns "diagnosis before the regional stage" and "diagnosis after the regional stage". Data limitations allowed for the calibration of a limited number of parameters per cancer type. Therefore, we assumed that the mean and standard deviations of the threshold volumes are equal (see "Tumour growth" section).

Secondly, we simultaneously calibrated the age- and cancer type-dependent malignant conversion rates and age boundaries of the survival functions (derived from the hazard functions, see section 1.1.4.1). The outcomes of the microsimulation model (no screening scenario) were fitted to German age and cancer type specific annual incidental lung cancer cases of the period 2010-2012[11]. The second calibration step was done separately for males and females.

The Nelder-Mead Simplex method implemented in the R package "FME"[18] was used to minimize squared residuals in both calibration steps.

1.3. Health economics

The costs per unit were obtained using EBM (Unit assessment scale applied in the German healthcare) or DRG (Diagnosis Related Groups) codes and are summarized in Table 8. The model includes CT-guided needle biopsy-induced pneumothorax as a complication that leads to increased costs of the staging tests.

Table S8: Cost per unit: screening and no screening

	Procedure	Code EBM* or DRG**	Costs per unit	Reference
Screening				
Screening	Low dose CT Screening	No yet available	150€ Values for the sensitivity analyses: I: 200€ ; II: 500€; III: 100€	Experts, [19]
Diagnostic work-up and Staging	CT-guided needle biopsy	EBM code 34505	103€	[20]
	Complication	DRG E76C	2,976.88€	[21,17,22]
	Histology (pathology)	EBM code 19310	8.41€	[20]
	Head magnetic resonance imaging (MRI)	EBM code 34410	126.59€	[20]
	Medical contrast medium for MRI	EBM code 34452	46.55€	[20]
No screening				
Diagnostic work-up and Staging	Positron emission tomography (PET)	EBM code 34701	589.95€	[20]
	Endobronchial ultrasound-guided trans bronchial needle aspiration (EBUS-TBNA)	EBM code 13662 or 09315	988.00€	[20]
	Histology (pathology)	EBM code 19310	8.41€	[20]
	Head MRI	EBM code 34410	126.59€	[20]
	Medical contrast medium for MRT	EBM code 34452	46.55€	[20]

* Unit assessment scale applied in the German healthcare
** Diagnosis Related Groups

In the calculations of the total cost of screening we did not include lifetime lung cancer treatment costs and the costs for pharmaceuticals. The reason of omitting these expenditures is that there is partly available German data on life time costs stratified across ages and cancer stages and histology. Therefore we made the assumptions based on the literature. We based these assessments on data given by Mc Guire et al. [23] who calculated the costs of non-small cell lung cancer for Germany, France and England.

The average treatment costs for patients with metastatic disease were 27,932€ for the first year and 22,909€ for the second year after the diagnoses. We used these values to calculate costs for people with the advanced cancers in our model output. For that we calculated the mean survival of the patients with stage III and IV which is 1.100702 years (50-75-15-9-NELSON-VDT400-V500). Based on the mean survival and the average costs for each year (Mc. Guire) we calculated treatment costs of 26,698€ for advanced cancers (stage III and IV).

Mc Guire et al.[23] do not provide cost data for people with the early-staged cancers. In order to determine relevant costs for the early-staged cancers we took data on the lifetime costs for people with the early-staged cancers in the UK calculated by the British Department of Health [24]. Based on their estimates we calculated the ratio between the costs given for I-II and III-IV stages: (i) ratio of costs between III and I stages is used to define a base case scenario. Under these assumptions total treatment costs for Stage I and II are 30,101€ and for stage III

and IV 45,808€ (example for 50-75-15-9-NELSON-VDT400-V500). In order to obtain the costs for people with early-stage cancer in our model we applied these ratios to the costs calculated based on the mean survival and the average costs for late cancers [23]. The same calculations were performed for each of the six evaluated scenarios and scenarios of the sensitivity analysis.

1.4. Sensitivity analysis

Parameter uncertainty:

We varied the nodule size-dependent sensitivity parameters of LDCT exam within a range of ±20%. The long term survival probability for the screened individuals – who were diagnosed at screening with lung cancer in stage I or II and who would die of the cancer in the non-screening scenario – was tested for the range of values: 20%, 30%, 50% and 60%. We decreased adherence for the next years after the initial screening to 85%.

Additional scenarios:

We prolonged the period of the screening program and simulated ten years of annual screening for each of the evaluated scenarios. The cost per LDCT unit varied across three different scenarios (Table 8). Additionally, the total costs were analyzed for a hypothetical scenario (scenario 4) when staging tests at screening were the same as at clinical settings in no screening scenario.

Because treatment costs are based on different assumptions we tested possible impacts of the treatment costs in the sensitivity analyses. In the pessimistic scenario the costs for Stage I and II are based on the ratio of costs between stage IV and I (see Table 9, example is given for 50-75-15-9-NELSON-VDT400-V500). In the last years a few cost inducing pharmaceutical drugs for lung cancer treatment have been developed and introduced to the market [25]. It is possible that they were not taken into the calculations by Mc Guirre et al. To account for that we added the third scenario with lifetime costs for the patients with the advanced cancer of 77,702€ [26] (see Table 9).

Table S9: Lifetime treatment costs for patients diagnosed with lung cancer by cancer stages calculated for 50-75-15-9-NELSON-VDT400-V500.

Stages	Lifetime costs (British department of health[23])	Max Scenario (Cost Ratio IV / I)	Min Scenario (Cost Ratio III / I)	Scenario with new treatment options
Stage I	7,135.00 £	45,803.38 €**	31,960.12 €**	118,234.97 €**
Stage II	7,135.00 £	45,803.38 €**	31,960.12 €**	118,234.97 €**
Stage III	6,720.00 £	30,101.20 €*	30,101.20 €*	77,702.00 €
Stage IV	4,689.00 £	30,101.20 €*	30,101.20 €*	77,702.00 €

*calculated based on the mean survival and the average costs for late cancers [23]
** calculated based on the cost ratios multiplied with the costs for people with the advanced cancers

2. Results

2.1. Calibration

Figure S1: Diagnosed lung cancer cases, Men, 2010.

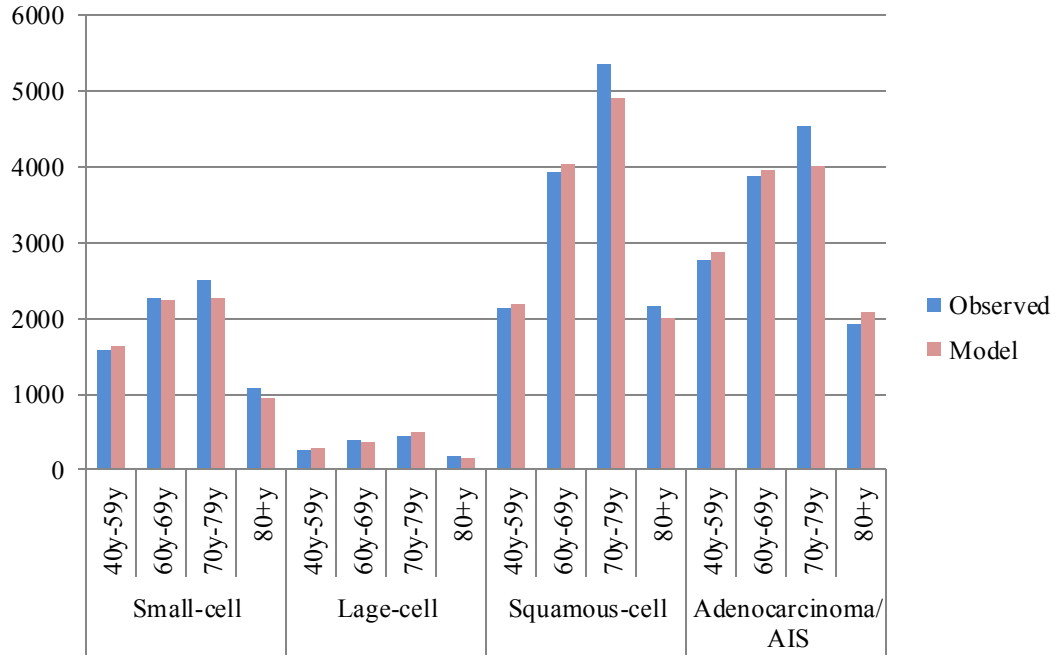


Figure S2: Diagnosed lung cancer cases, Men, 2011.

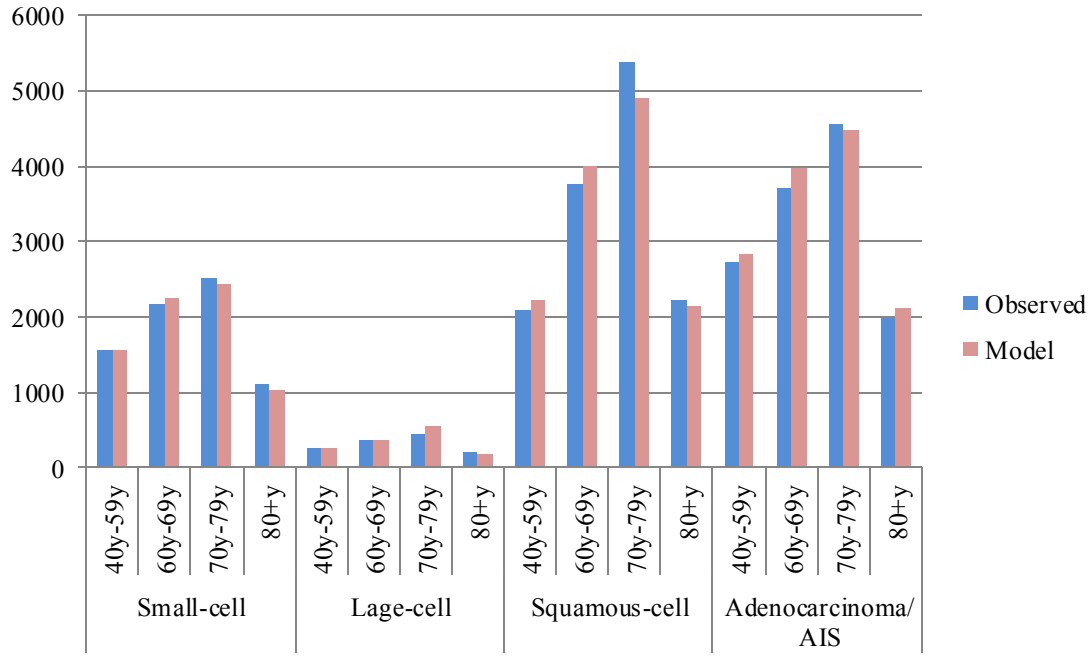


Figure S3: Diagnosed lung cancer cases, Men, 2012.

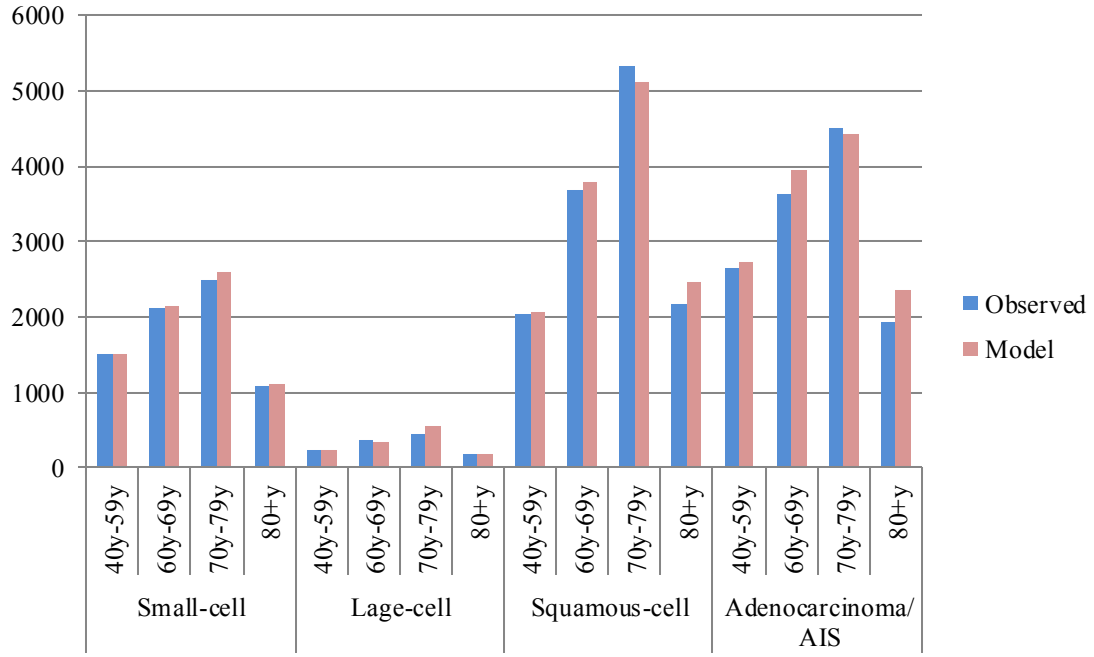


Figure S4: Diagnosed lung cancer cases, Women, 2010.

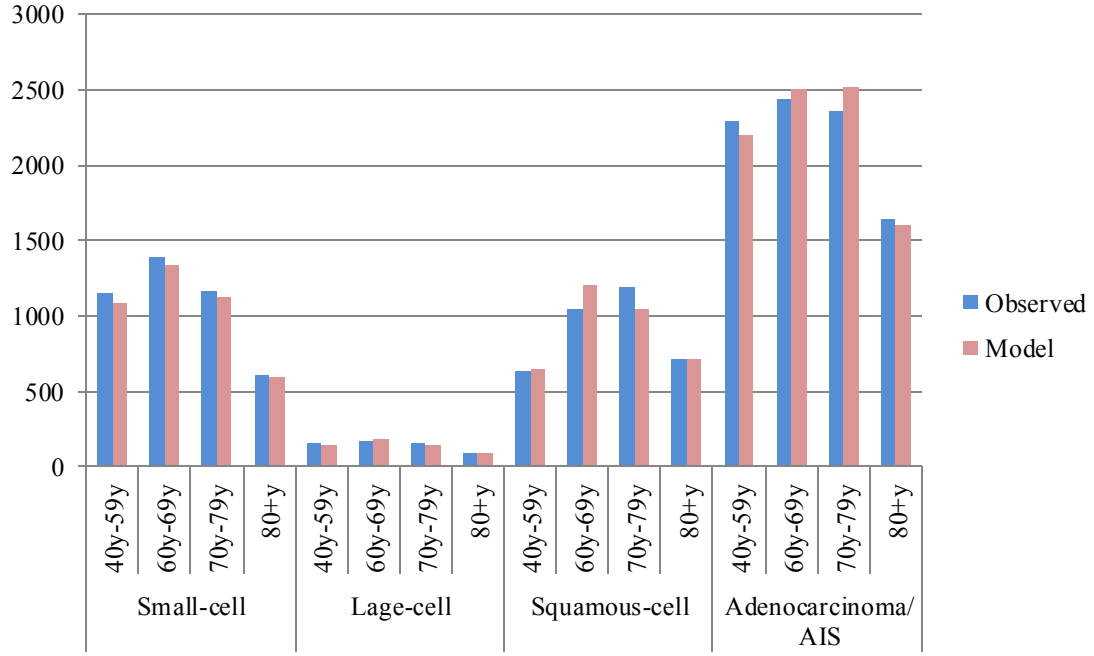


Figure S5: Diagnosed lung cancer cases, Women, 2011.

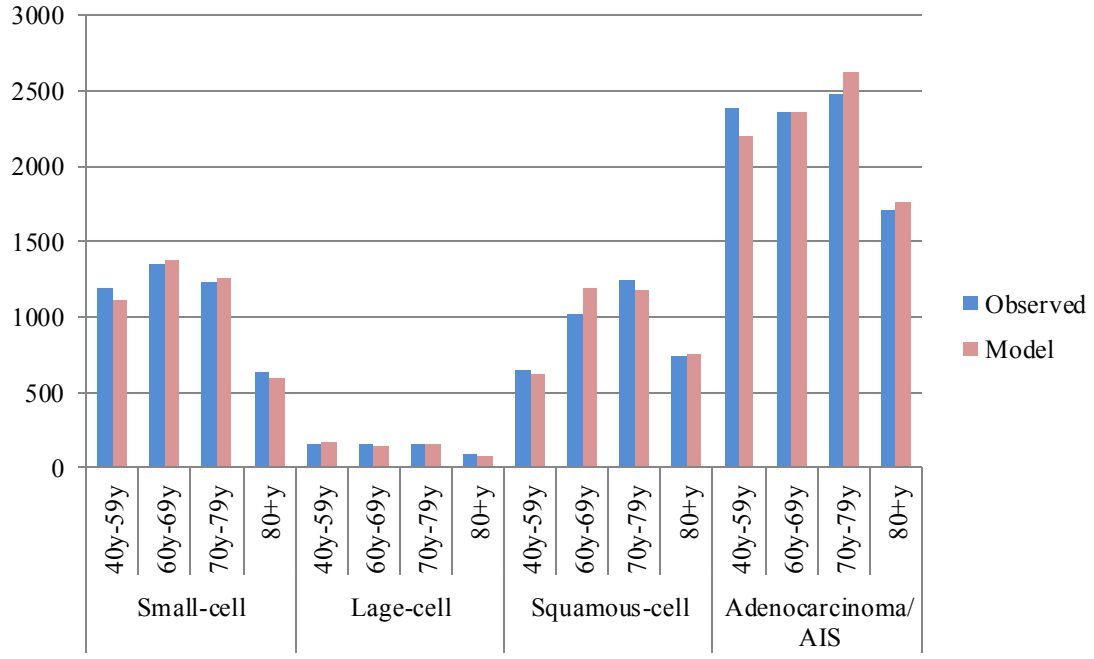
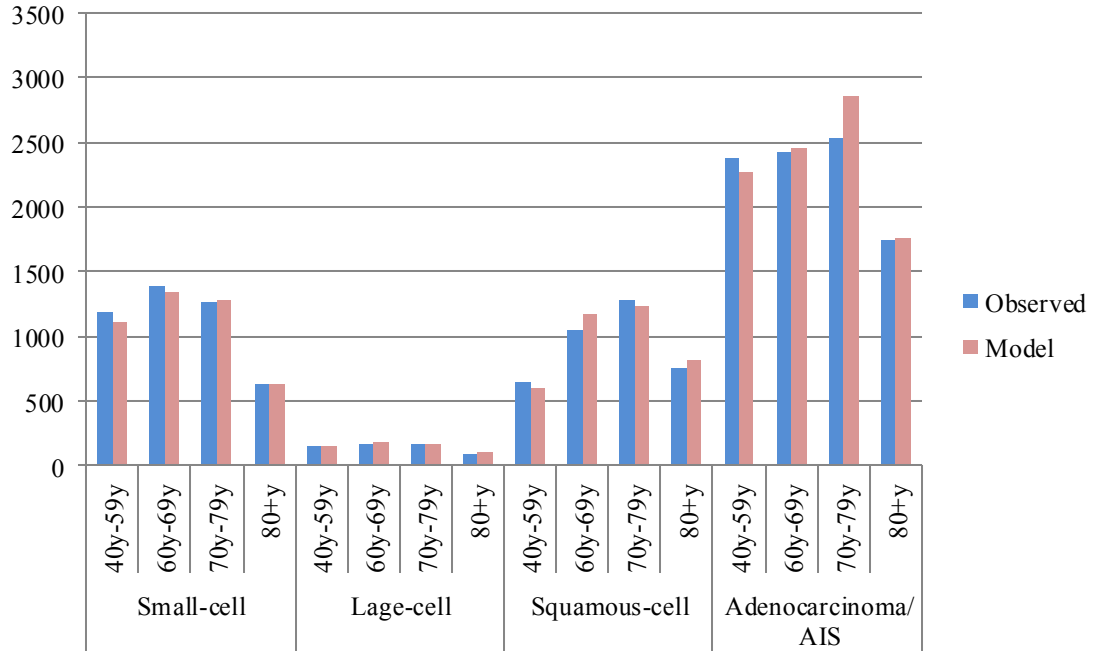


Figure S6: Diagnosed lung cancer cases, Women, 2012.



2.2. Benefits and harms of lung cancer screening for the baseline scenarios

Table S 10: Benefits and harms of lung cancer screening for the baseline scenarios

	50-75-15-9-NELSON-VDT400-V500	55-74-30-15-NELSON-VDT400-V500	50-75-15-9-NLST-GR10-D10	55-74-30-15-NLST-GR10-D10
Number of people screened	7,431,345	4,373,484	7,431,345	4,373,484
Screening outcomes				
Lung Cancer Findings	179,504	126,910	181,468	128,484
Screen detection Stage I	114,379	79,598	109,608	76,595
Screen detection Stage II	13,254	9,583	14,774	10,633
Screen detection Stage III	31,447	22,698	34,879	25,024
Screen detection Stage IV	20,424	15,031	22,207	16,232
Stage III, %	17.52	17.89	19.22	19.48
Stage IV, %	11.38	11.84	12.24	12.63
Total Cases Detected at an Early Stage	127,633	89,181	124,382	87,228
Total Cases Detected at an Early Stage, %	71.10	70.27	68.54	67.89
Small-cell carcinoma	10,048	6,601	10,528	6,915
Large-cell carcinoma	5,003	3,490	5,106	3,560
Squamous-cell carcinoma	42,688	29,549	43,182	29,873
Adenocarcinoma	92,003	64,423	91,697	64,209
Adenocarcinoma *in situ*	29,762	22,847	30,955	23,927
Small-cell carcinoma, %	5.60	5.20	5.80	5.38
Large-cell carcinoma, %	2.79	2.75	2.81	2.77
Squamous-cell carcinoma, %	23.78	23.28	23.80	23.25
Adenocarcinoma, %	51.25	50.76	50.53	49.97
Adenocarcinoma *in situ*, %	16.58	18.00	17.06	18.62
False-Positive Findings	262,311	185,356	4,531,519	3,208,432
False-Positive Findings of all screen detected findings	59.37	59.36	96.15	96.15
Interval cancer: False Negative Detection	33,111	21,763	32,101	21,106
Small-cell carcinoma	15,894	10,275	15,464	9,994
Large-cell carcinoma	1,576	1,044	1,520	1,005
Squamous-cell carcinoma	11,449	7,676	11,097	7,440
Adenocarcinoma	4,174	2,754	4,006	2,660
Adenocarcinoma *in situ*	18.00	14.00	14.00	7.00
Interval Cancer Stage I	5,363	3,556	5,147	3,413
Interval Cancer Stage II	1,810	1,211	1,765	1,182
Interval Cancer Stage III	8,745	5,619	8,467	5,439
Interval Cancer Stage IV	17,193	11,377	16,722	11,072
True Interval cancer	10,232	6,638	10,232	6,638
Small-cell carcinoma	8,494	5,504	8,494	5,504
Large-cell carcinoma	201	142	201	142
Squamous-cell carcinoma	1,517	981	1,517	981
Adenocarcinoma	20.00	11.00	20.00	11.00
Adenocarcinoma *in situ*	0.00	0.00	0.00	0.00
Interval Cancer Stage I	818	535.00	818	535
Interval Cancer Stage II	389	263	389	263
Interval Cancer Stage III	2,594	1,683	2,594	1,683
Interval Cancer Stage IV	6,431	4,157	6,431	4,157
Small-cell carcinoma, % of interval cancers	56.27	55.56	56.59	55.86
Stage IV, % of interval cancers	54.50	54.70	54.69	54.89
Clinical Detection	771,760	435,763	770,918	435,228
Clinical Detection: onset of cancer before the end of screening	208,902	137,329	208,060	136,794
All detected cancers: onset of cancer before the end of screening	388,406	264,239	389,528	265,278
Overdiagnosis	31,005	23,772	31,385	24,260
Overdiagnosis, % of screening detected cases	17.27	18.73	17.30	18.88
Small-cell carcinoma	51.00	33.00	52.00	35.00
Large-cell carcinoma	147	110.00	144	105
Squamous-cell carcinoma	1,683	1,201	1,606	1,155
Adenocarcinoma	6,429	4,795	5,934	4,461
Adenocarcinoma *in situ*	22,695	17,633	23,649	18,504
Adenocarcinoma *in situ*, %	73.20	74.18	75.35	76.27
Overdiagnosis Stage I	19,722	14,434	19,282	14,369
Overdiagnosis Stage II	2,368	1,919	2,603	2,090
Overdiagnosis Stage III	5,613	4,573	6,141	4,916
Overdiagnosis Stage IV	3,302	2,846	3,359	2,885
Radiation-induced Lung Cancer Deaths	2,390	1,329	2,388	1,328
No screening scenario				
Clinical Detection no screening	919,585	538,385	919,585	538,385
Clinical Detection Stage 1	132,312	77,379	132,312	77,379
Clinical Detection Stage 2	56,328	33,417	56,328	33,417
Clinical Detection Stage 3	235,578	138,090	235,578	138,090
Clinical Detection Stage 4	495,367	289,499	495,367	289,499
Clinical Detection: onset of cancer before the end of screening	356,727	239,951	356,727	239,951

Table S 11: Benefits and harms of lung cancer screening for the baseline scenarios (continued)

	50-75-15-9-NELSON-VDT400-V500	55-74-30-15-NELSON-VDT400-V500	50-75-15-9-NLST-GR10-D10	55-74-30-15-NLST-GR10-D10
Clinical detection during the first five years: Histological class	152,040	102,786	152,040	102,786
Small-cell carcinoma	35,472	23,234	35,472	23,234
Large-cell carcinoma	6,265	4,321	6,265	4,321
Squamous-cell carcinoma	48,009	32,720	48,009	32,720
Adenocarcinoma	59,673	40,630	59,673	40,630
Adenocarcinoma *in situ*	2,621	1,881	2,621	1,881
Clinical Detection Stage 1	22,129	15,039	22,129	15,039
Clinical Detection Stage 2	9,129	6,247	9,129	6,247
Clinical Detection Stage 3	38,797	26,004	38,797	26,004
Clinical Detection Stage 4	81,985	55,496	81,985	55,496
Deaths from lung cancer				
Death from lung cancer: screening	763,653	442,246	764,847	443,061
Death from lung cancer: onset of cancer before the end of screening	275,110	184,150	276,304	184,965
Death from lung cancer: no screening	800,040	467,246	800,040	467,246
Death from lung cancer: no screening (onset of cancer before the end of screening)	311,497	209,150	311,497	209,150
Mortality reduction vs no screening, %	**11.68**	**11.95**	**11.30**	**11.56**
Benefits of screening vs no screening				
Averted death vs no screening	**36,387**	**25,000**	**35,193**	**24,185**
Life years gained vs no screening	541,697	356,262	525,811	345,918
Life years gained vs no screening: 3% discount	**355,348**	**236,371**	**346,100**	**230,284**
Life years gained vs no screening: 1.5% discount	435,161	288,028	423,115	280,136
Healthcare resources for the screening program				
Number of Screen exams	29,969,925	16,660,175	29,955,605	16,650,031
Number of Follow-up scans	2,781,924	1,525,291	4,011,903	2,839,342
Number of Follow-up scans: malignant nodules	100,296	71,876	157,843	110,595
Number of Work-ups	441,815	312,266	945,678	669,564
Number of Work-ups: malignant nodules	171,637	121,317	173,250	122,633
Number of Complications	117,474	82,898	233,375	165,097
Efficiency of screening				
Detected cancer per 1000 scans	5.99	7.62	6.06	7.72
Interval cancers per 1000 screen-scans	1.45	1.70	1.41	1.67
Lung cancer deaths per 1000 screen-scans: onset of cancer before the end of screening	9.18	11.05	9.22	11.11
Averted lung cancer deaths vs no screening per 1000 screen-scans	1.21	1.50	1.17	1.45
Life years gained (3% discount) vs no screening per 1000 screen-scans	11.86	14.19	11.55	13.83
Health economics outcomes of screening vs no screening				
Total costs (discounted)	29363651302	17776335686	29885787583	18223237851
Total costs: no screening(discounted)	21900234274	13183590963	21900234274	13183590963
Additional costs vs. no screening (discounted)	7463417028	4592744723	7985553310	5039646887
ACER: Costs (including life time treatment costs) per Life Year Gained (uniform discounting) vs no screening	21,003	19,430	23,072	21,884
Cost categories (Discounted 3%)				
Screening scans	4,243,729,151	2,355,013,913	4,241,738,728	2,353,604,382
Work-up total malignant	211,365,526	149,013,209	212,913,711	150,313,048
Complication	178,066,109	125,439,507	179,259,484	126,453,389
Without complication	33,299,417	23,573,702	33,654,226	23,859,659
Follow-up malignant	15,044,522	10,781,399	23,676,532	16,589,331
False-Positive Work-up total	201,146,272	142,104,689	580,683,348	411,030,986
Complication	179,465,545	126,787,810	518,093,885	366,727,652
Without complication	21,680,726	15,316,878	62,589,462	44,303,334
False-Positive Follow-up	385,177,551	208,247,816	550,582,775	389,724,592
Interval cancer: False-Negative Detection	55,046,074	36,158,088	53,381,576	35,078,201
True Interval cancer	16,964,750	10,988,952	16,964,750	10,988,952
Treatment	24,235,177,456	14,864,027,620	24,205,846,163	14,855,908,359

Figure S7: Accumulated lung cancer death cases 50-75-15-9-NELSON-VDT400-V500 vs. 50-75-15-9-NLST-GR10-D10

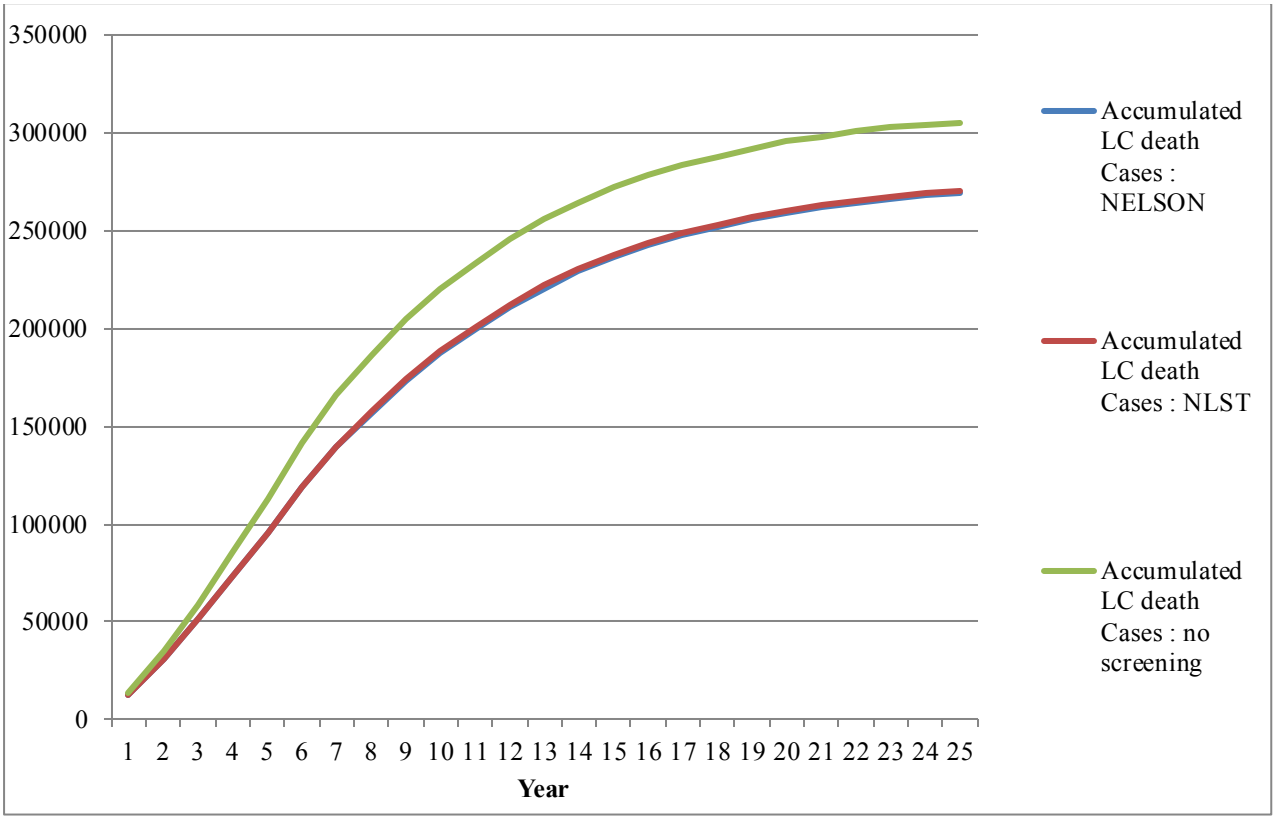
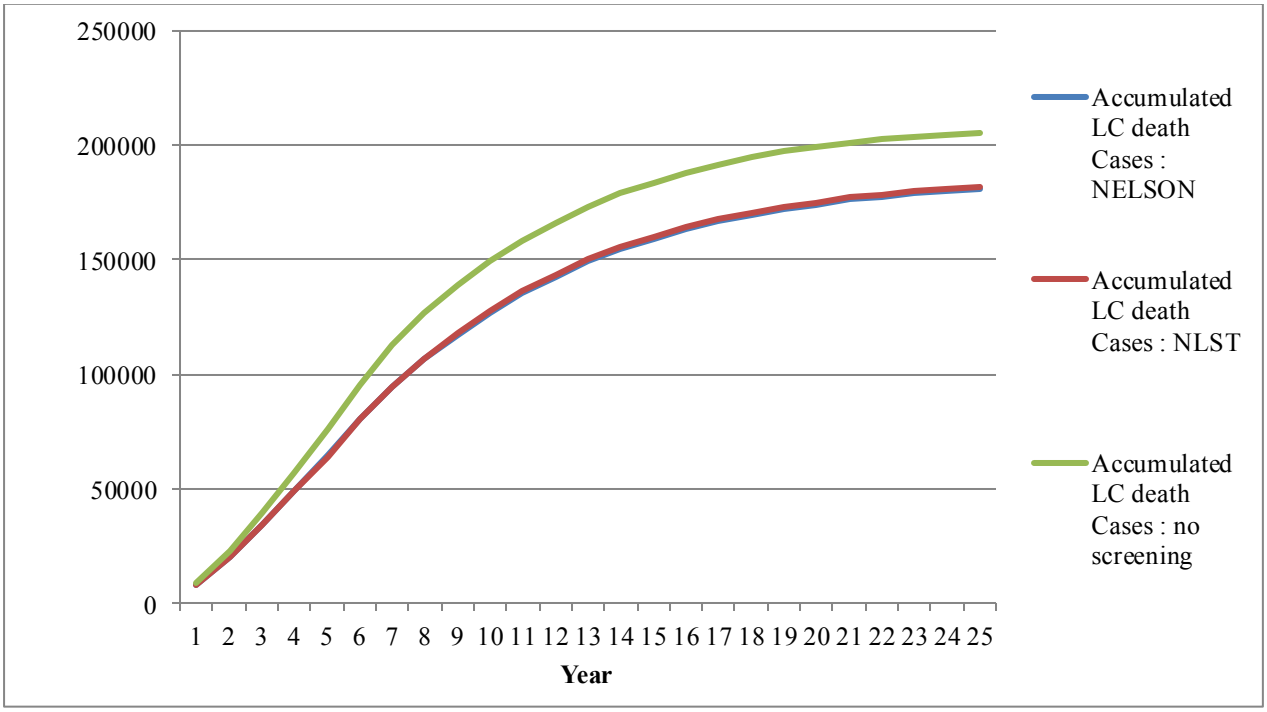


Figure S8: Accumulated lung cancer death cases 55-74-30-15-NELSON-VDT400-V500 vs. 55-74-30-15-NLST-GR10-D10



2.3. Main outcomes and Cost-effectiveness of the 76 baseline screening scenarios.

Table S12: Main outcomes and Cost-effectiveness of the 76 baseline screening scenarios.

Scenario	Scenario characteristics	Detected cancers at an early stage (I/II), %	Reduction in lung cancer mortality, %	Lung cancer deaths averted	Discounted life years gained	Interval cancer cases	Over diagnosed cases	Over diagnosis, %	Discounted total cost, million Euro	Discounted additional costs vs no screening, million Euro	Cost per life years gained vs no screening (uniform discounting) Euro	Discounted cost per lung cancer death averted vs no screening, Euro	ICER vs the previous efficient scenario, Euro per LYG	ICER vs the previous efficient scenario, Euro per averted lung cancer death
Scenario 65	55-75-40-10-NELSON-VDT300-none	67.31	9.95	14,373	133,222	23,057	6,733	9.48	10,892,118,387	2,231,946,546	16,754	155,287	16,754	155,287
Scenario 64	55-75-40-10-NELSON-VDT400-none	67.95	10.65	15,395	140,490	21,367	9,184	11.73	11,056,787,394	2,396,615,552	17,059	155,675	not efficient	161,124
Scenario 66	55-75-40-10-NELSON-VDT600-none	68.25	11.00	15,891	143,763	20,406	12,036	14.35	11,211,978,121	2,551,806,280	17,750	160,582	not efficient	not efficient
Scenario 75	55-75-40-10-NLST-GR12.5-none	67.50	11.37	16,430	147,652	19,629	15,341	17.20	11,716,673,226	3,056,501,385	20,701	186,032	not efficient	not efficient
Scenario 73	55-75-40-10-NLST-GR10-none	67.91	11.52	16,638	149,484	19,570	16,074	17.75	11,766,309,036	3,106,137,195	20,779	186,689	not efficient	not efficient
Scenario 74	55-75-40-10-NLST-GR7.5-none	68.20	11.63	16,798	150,829	19,514	16,812	18.34	11,811,094,697	3,150,922,856	20,891	187,577	not efficient	not efficient
Scenario 76	55-75-40-10-NLST-Dfup5	67.08	11.26	16,270	151,944	20,278	16,476	18.90	11,712,212,808	3,052,040,967	20,087	187,587	not efficient	not efficient
Scenario 67	55-75-40-10-NELSON-Vfup80	68.43	11.49	16,604	154,199	20,558	16,389	18.92	11,381,642,165	2,721,470,324	17,649	163,905	not efficient	not efficient
Scenario 72	55-75-40-10-NLST-GR12.5-D10	66.61	11.48	16,594	154,561	19,424	17,268	19.07	11,789,031,396	3,128,859,555	20,243	188,554	not efficient	not efficient
Scenario 70	55-75-40-10-NLST-GR10-D11	66.84	11.59	16,741	155,308	19,429	17,366	19.11	11,800,360,566	3,140,188,725	20,219	187,575	not efficient	not efficient
Scenario 68	55-75-40-10-NLST-GR10-D10	67.69	11.75	16,976	157,701	19,409	17,467	19.19	11,817,384,038	3,157,212,197	20,020	185,981	not efficient	not efficient
Scenario 59	55-75-40-10-NELSON-VDT400-V750	68.73	11.90	17,201	158,585	19,883	16,598	18.63	11,416,918,590	2,756,746,749	17,383	160,267	not efficient	not efficient
Scenario 71	55-75-40-10-NLST-GR7.5-D10	68.35	11.90	17,200	159,297	19,404	17,647	19.30	11,838,944,522	3,178,772,681	19,955	184,812	not efficient	not efficient
Scenario 69	55-75-40-10-NLST-GR10-D9	68.50	11.91	17,212	159,963	19,392	17,575	19.27	11,834,207,265	3,174,035,423	19,842	184,408	not efficient	not efficient
Scenario 62	55-75-40-10-NELSON-VDT300-V500	69.95	12.14	17,542	161,967	19,866	17,162	19.09	11,459,390,353	2,799,218,512	17,283	159,572	not efficient	not efficient
Scenario 58	55-75-40-10-NELSON-VDT400-V500	70.07	12.16	17,564	162,073	19,862	17,221	19.14	11,465,748,287	2,805,576,446	17,311	159,734	not efficient	not efficient
Scenario 63	55-75-40-10-NELSON-VDT600-V500	70.30	12.19	17,608	162,281	19,857	17,656	19.49	11,491,382,892	2,831,211,051	17,446	160,791	not efficient	not efficient
Scenario 61	55-75-40-10-NELSON-VDT400-V400	70.71	12.27	17,726	163,470	19,857	17,573	19.42	11,491,130,432	2,830,958,591	17,318	159,707	not efficient	not efficient
Scenario 60	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	19.69	11,515,704,974	2,855,533,133	17,321	159,625	19,707	184,009
Scenario 8	55-74-30-15-NELSON-VDT300-none	67.41	9.72	20,335	192,747	33,009	9,106	9.12	16,964,229,032	3,780,638,069	19,615	185,918	not efficient	not efficient
Scenario 7	55-74-30-15-NELSON-VDT400-none	68.13	10.47	21,908	204,456	30,527	12,562	11.37	17,202,833,077	4,019,242,114	19,658	183,460	not efficient	not efficient
Scenario 27	55-80-30-15-NELSON-VDT300-none	67.52	10.10	23,029	207,468	38,212	11,724	10.14	17,709,501,637	4,159,369,822	20,048	180,614	not efficient	not efficient
Scenario 9	55-74-30-15-NELSON-VDT600-none	68.49	10.82	22,633	209,464	29,157	16,599	14.01	17,425,676,762	4,242,085,799	20,252	187,429	not efficient	not efficient
Scenario 18	55-74-30-15-NLST-GR12.5-none	67.86	11.21	23,437	215,599	28,049	21,270	16.88	18,086,156,020	4,902,565,056	22,739	209,181	not efficient	not efficient
Scenario 16	55-74-30-15-NLST-GR10-none	68.21	11.35	23,747	218,277	27,972	22,232	17.39	18,153,904,252	4,970,313,288	22,771	209,303	not efficient	not efficient
Scenario 17	55-74-30-15-NLST-GR7.5-none	68.46	11.46	23,962	220,191	27,900	23,237	17.96	18,215,134,331	5,031,543,367	22,851	209,980	not efficient	not efficient
Scenario 26	55-80-30-15-NELSON-VDT400-none	68.24	10.93	24,917	220,616	35,048	16,282	12.62	18,002,132,447	4,452,000,631	20,180	178,673	not efficient	not efficient
Scenario 19	55-74-30-15-NLST-Dfup5	67.28	11.07	23,152	221,728	28,955	22,938	18.63	18,078,388,416	4,894,797,453	22,076	211,420	not efficient	not efficient
Scenario 10	55-74-30-15-NELSON-Vfup80	68.62	11.29	23,620	224,880	29,359	22,740	18.59	17,662,309,284	4,478,718,321	19,916	189,616	not efficient	not efficient
Scenario 15	55-74-30-15-NLST-GR12.5-D10	66.85	11.31	23,646	225,756	27,773	24,000	18.76	18,184,707,034	5,001,116,071	22,153	211,499	not efficient	not efficient
Scenario 28	55-80-30-15-NELSON-VDT600-none	68.57	11.35	25,871	226,617	33,118	21,861	15.63	18,293,791,730	4,743,659,914	20,932	183,358	not efficient	not efficient
Scenario 13	55-74-30-15-NLST-GR10-D11	67.05	11.39	23,831	226,640	27,773	24,145	18.81	18,200,613,216	5,017,022,253	22,136	210,525	not efficient	not efficient
Scenario 11	55-74-30-15-NLST-GR10-D10	67.89	11.56	24,185	230,284	27,744	24,260	18.88	18,223,237,851	5,039,646,887	21,885	208,379	not efficient	not efficient

Scenario 2	55-74-30-15-NELSON-VDT400-V750	68.89	11.69	24,442	231,099	28,431	22,874	18.22	17,705,725,213	4,522,134,250	19,568	185,015	not efficient	not efficient
Scenario 14	55-74-30-15-NLST-GR7.5-D10	68.57	11.72	24,512	232,766	27,736	24,493	18.99	18,253,498,654	5,069,907,690	21,781	206,834	not efficient	not efficient
Scenario 37	55-80-30-15-NLST-GR12.5-none	67.77	11.72	26,719	232,797	31,764	28,055	18.78	19,112,331,877	5,562,200,062	23,893	208,174	not efficient	not efficient
Scenario 12	55-74-30-15-NLST-GR10-D9	68.72	11.73	24,527	233,603	27,721	24,418	18.97	18,247,633,560	5,064,042,597	21,678	206,468	not efficient	not efficient
Scenario 35	55-80-30-15-NLST-GR10-none	68.13	11.89	27,092	235,833	31,657	29,431	19.39	19,199,988,990	5,649,857,174	23,957	208,543	not efficient	not efficient
Scenario 5	55-74-30-15-NELSON-VDT300-V500	70.15	11.94	24,973	236,226	28,407	23,689	18.68	17,767,037,281	4,583,446,318	19,403	183,536	not efficient	not efficient
Scenario 1	55-74-30-15-NELSON-VDT400-V500	70.27	11.95	25,000	236,371	28,401	23,772	18.73	17,776,335,686	4,592,744,723	19,430	183,710	not efficient	not efficient
Scenario 6	55-74-30-15-NELSON-VDT600-V500	70.52	11.98	25,059	236,665	28,392	24,434	19.12	17,814,338,122	4,630,747,159	19,567	184,794	not efficient	not efficient
Scenario 36	55-80-30-15-NLST-GR7.5-none	68.34	12.00	27,350	238,024	31,556	30,922	20.08	19,284,015,000	5,733,883,184	24,090	209,648	not efficient	not efficient
Scenario 4	55-74-30-15-NELSON-VDT400-V400	70.90	12.06	25,223	238,424	28,393	24,278	19.03	17,812,380,227	4,628,789,264	19,414	183,515	not efficient	not efficient
Scenario 3	55-74-30-15-NELSON-VDT400-V300	71.58	12.18	25,467	240,626	28,389	24,767	19.32	17,849,042,023	4,665,451,059	19,389	183,196	not efficient	not efficient
Scenario 38	55-80-30-15-NLST-Dfup5	66.76	11.67	26,589	240,683	32,739	31,090	21.03	19,160,111,768	5,609,979,952	23,309	210,989	not efficient	not efficient
Scenario 29	55-80-30-15-NELSON-Vfup80	68.00	11.89	27,104	244,027	33,178	30,722	20.93	18,625,060,345	5,074,928,530	20,797	187,239	not efficient	not efficient
Scenario 34	55-80-30-15-NLST-GR12.5-D10	66.35	11.89	27,105	244,796	31,380	32,411	21.15	19,281,610,562	5,731,478,747	23,413	211,455	not efficient	not efficient
Scenario 32	55-80-30-15-NLST-GR10-D11	66.56	11.98	27,308	245,671	31,391	32,590	21.19	19,299,330,176	5,749,198,361	23,402	210,532	not efficient	not efficient
Scenario 30	55-80-30-15-NLST-GR10-D10	67.37	12.16	27,706	249,634	31,348	32,764	21.27	19,325,894,027	5,775,762,212	23,137	208,466	not efficient	not efficient
Scenario 21	55-80-30-15-NELSON-VDT400-V750	68.19	12.28	27,987	250,445	32,125	30,739	20.47	18,661,518,852	5,111,387,037	20,409	182,634	not efficient	not efficient
Scenario 33	55-80-30-15-NLST-GR7.5-D10	68.04	12.31	28,062	252,243	31,338	33,098	21.40	19,361,758,630	5,811,626,814	23,040	207,100	not efficient	not efficient
Scenario 31	55-80-30-15-NLST-GR10-D9	68.18	12.32	28,080	253,130	31,313	32,991	21.38	19,354,607,603	5,804,475,788	22,931	206,712	not efficient	not efficient
Scenario 24	55-80-30-15-NELSON-VDT300-V500	69.49	12.55	28,596	256,006	32,094	31,929	21.02	18,741,364,602	5,191,232,786	20,278	181,537	not efficient	not efficient
Scenario 20	55-80-30-15-NELSON-VDT400-V500	69.61	12.56	28,625	256,159	32,086	32,050	21.08	18,752,973,157	5,202,841,342	20,311	181,759	not efficient	not efficient
Scenario 25	55-80-30-15-NELSON-VDT600-V500	69.89	12.59	28,694	256,478	32,077	32,983	21.53	18,803,698,202	5,253,566,386	20,483	183,089	not efficient	not efficient
Scenario 23	55-80-30-15-NELSON-VDT400-V400	70.25	12.67	28,877	258,339	32,076	32,752	21.42	18,798,713,288	5,248,581,472	20,317	181,756	not efficient	not efficient
Scenario 22	55-80-30-15-NELSON-VDT400-V300	70.95	12.80	29,165	260,807	32,071	33,473	21.76	18,846,402,156	5,296,270,341	20,307	181,597	not efficient	216,454
Scenario 46	50-75-15-9-NELSON-VDT300-none	67.40	9.68	30,147	295,093	48,838	13,432	9.09	28,347,809,378	6,447,575,105	21,849	213,871	not efficient	not efficient
Scenario 45	50-75-15-9-NELSON-VDT400-none	68.06	10.27	31,994	308,862	45,891	17,943	11.18	28,650,791,510	6,750,557,237	21,856	210,994	not efficient	not efficient
Scenario 47	50-75-15-9-NELSON-VDT600-none	68.37	10.54	32,825	314,731	44,293	22,752	13.41	28,917,092,962	7,016,858,689	22,295	213,766	not efficient	not efficient
Scenario 56	50-75-15-9-NLST-GR12.5-none	68.06	10.95	34,122	325,575	42,717	28,483	15.84	29,748,996,225	7,848,761,952	24,107	230,021	not efficient	not efficient
Scenario 54	50-75-15-9-NLST-GR10-none	68.40	11.08	34,525	329,167	42,610	29,643	16.29	29,830,458,906	7,930,224,633	24,092	229,695	not efficient	not efficient
Scenario 55	50-75-15-9-NLST-GR7.5-none	68.64	11.16	34,757	331,214	42,520	30,791	16.76	29,902,320,995	8,002,086,722	24,160	230,229	not efficient	not efficient
Scenario 57	50-75-15-9-NLST-Dfup5	68.05	10.83	33,738	333,574	44,213	29,610	17.04	29,682,843,414	7,782,609,141	23,331	230,678	not efficient	not efficient
Scenario 48	50-75-15-9-NELSON-Vfup80	69.39	11.02	34,317	337,355	44,808	29,451	17.05	29,191,246,090	7,291,011,817	21,612	212,461	not efficient	not efficient
Scenario 53	50-75-15-9-NLST-GR12.5-D10	67.49	11.05	34,418	339,475	42,368	30,993	17.17	29,828,497,218	7,928,262,945	23,355	230,352	not efficient	not efficient
Scenario 51	50-75-15-9-NLST-GR10-D11	67.69	11.13	34,673	340,726	42,383	31,253	17.24	29,854,521,936	7,954,287,663	23,345	229,409	not efficient	not efficient
Scenario 49	50-75-15-9-NLST-GR10-D10	68.54	11.30	35,193	346,100	42,333	31,385	17.30	29,885,787,583	7,985,553,310	23,073	226,907	not efficient	not efficient
Scenario 40	50-75-15-9-NELSON-VDT400-V750	69.77	11.43	35,603	347,754	43,379	29,951	16.83	29,273,891,072	7,373,656,799	21,204	207,108	not efficient	not efficient
Scenario 52	50-75-15-9-NLST-GR7.5-D10	69.17	11.44	35,622	349,465	42,322	31,706	17.41	29,926,417,893	8,026,183,620	22,967	225,315	not efficient	not efficient
Scenario 50	50-75-15-9-NLST-GR10-D9	69.37	11.45	35,669	350,891	42,301	31,560	17.37	29,918,079,355	8,017,845,082	22,850	224,785	not efficient	not efficient
Scenario 43	50-75-15-9-NELSON-VDT300-V500	71.00	11.67	36,352	355,128	43,349	30,891	17.22	29,351,505,809	7,451,271,536	20,982	204,976	not efficient	not efficient
Scenario 39	50-75-15-9-NELSON-VDT400-V500	71.10	11.68	36,387	355,348	43,343	31,005	17.27	29,363,651,302	7,463,417,029	21,003	205,112	not efficient	not efficient
Scenario 44	50-75-15-9-NELSON-VDT600-V500	71.30	11.71	36,465	355,742	43,335	31,770	17.60	29,408,338,707	7,508,104,434	21,105	205,899	not efficient	not efficient
Scenario 42	50-75-15-9-NELSON-VDT400-V400	71.72	11.78	36,709	358,394	43,334	31,596	17.52	29,409,436,683	7,509,202,410	20,952	204,560	not efficient	not efficient
Scenario 41	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	29,455,834,679	7,555,600,405	20,870	203,792	23,837	285,630

The scenarios are sorted arranging life years gained in ascending order.

2.4. Cost-effectiveness of the efficient screening scenarios in the sensitivity analyses

Table S13: Cost-effectiveness of the efficient screening scenarios in the sensitivity analyses.

Sensitivity analysis assumption	Scenario characteristics	Detected cancers at an early stage (I/II), %	Reduction in lung cancer mortality, %	Lung cancer deaths averted	Discounted life years gained	Interval cancer cases	Over diagnosed cases	Over diagnosis, %	Discounted total cost, million Euro	Discounted additional costs vs no screening, million Euro	Cost per life years gained vs no screening (uniform discounting) Euro	Discounted cost per lung cancer death averted vs no screening, Euro
Decreased adherence (85%)	55-75-40-10-NELSON-VDT300-only	67.88	11.04	15,951	147,905	18,266	14,241	17.51	11,128,381,492	2,468,209,650	16,687.80	154,736.99
	55-75-40-10-NELSON-VDT400-V300	70.48	11.71	16,926	154,633	17,939	17,447	19.99	11,327,266,138	2,667,094,296	17,247.89	157,573.81
	50-75-15-9-NELSON-VDT400-V300	71.59	11.20	34,885	339,158	39,059	31,360	18.12	28,876,917,490	6,976,683,217	20,570.59	199,990.92
Decreased CT sensitivity	55-75-40-10-NELSON-VDT300-only	65.91	8.51	12,290	113,926	28,728	5,822	9.40	10,769,522,882	2,109,351,040	18,515.04	171,631.49
	55-75-40-10-NELSON-VDT400-V300	69.81	10.75	15,538	142,709	25,783	16,697	20.53	11,362,508,546	2,702,336,704	18,935.96	173,917.92
	50-75-15-9-NELSON-VDT400-V300	70.76	10.31	32,114	312,327	55,624	30,160	18.61	29,154,812,658	7,254,578,384	23,227.53	225,900.80
Increased CT sensitivity	55-75-40-10-NELSON-VDT300-only	68.97	10.42	15,061	139,346	22,429	7,189	9.82	10,946,629,549	2,286,457,708	16,408.45	151,813.14
	55-75-40-10-NELSON-VDT400-V300	72.33	12.81	18,507	170,216	19,258	18,347	19.72	11,566,774,883	2,906,603,041	17,075.97	157,054.25
	50-75-15-9-NELSON-VDT400-V300	73.41	12.34	38,450	375,036	41,991	33,020	17.80	29,561,115,978	7,660,881,704	20,427.06	199,242.70
Survival 20%	55-75-40-10-NELSON-VDT300-only	67.31	4.90	7,073	64,976	23,057	6,733	9.48	10,892,118,388	2,231,946,546	34,350.47	315,558.68
	55-75-40-10-NELSON-VDT400-V300	71.35	6.15	8,886	81,476	19,854	17,892	19.69	11,515,704,975	2,855,533,133	35,047.54	321,351.92
	50-75-15-9-NELSON-VDT400-V300	72.39	5.90	18,383	179,031	43,331	32,183	17.78	29,455,834,680	7,555,600,406	42,202.87	411,010.19
Survival 30%	55-75-40-10-NELSON-VDT300-only	67.31	7.39	10,671	98,141	23,057	6,733	9.48	10,892,118,388	2,231,946,546	22,742.13	209,160.02
	55-75-40-10-NELSON-VDT400-V300	71.35	9.25	13,372	122,191	19,854	17,892	19.69	11,515,704,975	2,855,533,133	23,369.47	213,545.70
	50-75-15-9-NELSON-VDT400-V300	72.39	8.85	27,577	268,594	43,331	32,183	17.78	29,455,834,680	7,555,600,406	28,130.18	273,981.96
Survival 50%	55-75-40-10-NELSON-VDT300-only	67.31	12.31	17,788	163,572	23,057	6,733	9.48	10,892,118,388	2,231,946,546	13,645.04	125,474.85
	55-75-40-10-NELSON-VDT400-V300	71.35	15.38	22,218	203,495	19,854	17,892	19.69	11,515,704,975	2,855,533,133	14,032.47	128,523.41
	50-75-15-9-NELSON-VDT400-V300	72.39	14.76	45,972	448,474	43,331	32,183	17.78	29,455,834,680	7,555,600,406	16,847.36	164,352.22
Survival 60%	55-75-40-10-NELSON-VDT300-only	67.31	17.34	21,349	196,872	23,057	6,733	9.48	10,892,118,388	2,231,946,546	11,337.03	104,545.72
	55-75-40-10-NELSON-VDT400-V300	71.35	22.64	26,676	245,212	19,854	17,892	19.69	11,515,704,975	2,855,533,133	11,645.18	107,045.03
	50-75-15-9-NELSON-VDT400-V300	72.39	21.69	55,518	541,052	43,331	32,183	17.78	29,455,834,680	7,555,600,406	13,964.66	136,092.81
Cost per CT200 Euro	55-75-40-10-NELSON-VDT300-only	67.31	9.95	14,373	133,222	23,057	6,733	9.48	11,348,079,792	2,687,907,951	20,176.16	187,010.92
	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	19.69	11,971,666,380	3,311,494,538	20,086.20	185,113.45
	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	31,003,818,424	9,103,584,150	25,145.34	245,545.09
Cost per CT500 Euro	55-75-40-10-NELSON-VDT300-only	67.31	9.95	14,373	133,222	23,057	6,733	9.48	14,083,848,222	5,423,676,380	40,711.57	377,351.73
	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	19.69	14,707,434,810	6,047,262,968	36,680.28	338,043.66
	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	40,291,720,874	18,391,486,601	50,799.80	496,061.68
Cost per CT100 Euro	55-75-40-10-NELSON-VDT300-only	67.31	9.95	14,373	133,222	23,057	6,733	9.48	10,436,156,983	1,775,985,141	13,331.02	123,563.98
	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	19.69	11,059,743,569	2,399,571,727	14,554.84	134,136.72
	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	27,907,850,938	6,007,616,665	16,593.86	162,039.56
Innovative Treatment Cost	55-75-40-10-NELSON-VDT300-only	67.31	9.95	14,373	133,222	23,057	6,733	9.48	25,486,357,786	3,539,339,140	26,567.23	246,249.16
	55-75-40-10-NELSON-VDT400-V300	71.35	12.38	17,889	164,864	19,854	17,892	19.69	27,055,830,817	5,108,812,172	30,988.01	285,584.00
	50-75-15-9-NELSON-VDT400-V300	72.39	11.90	37,075	362,039	43,331	32,183	17.78	66,668,886,830	11,873,009,409	32,794.87	320,243.00

Table S 14: Comparison of the microsimulation model outcomes with the data from the NLST trial.

	NLST	55-74-30-15-NLST-GR10-D10
Follow-up after end of annual screening	median 6.5 years	7 years*
Screen exams per person	2.8	3.8
Lung Cancer specific mortality rate per 100,000 person-years:		
LDCT	247	332
Radiography/no screening	309	394
Difference in mortality rates	62	62
Lung cancer mortality reduction, %	20.1	15.8
All-cause mortality rate per 100,000 person-years		
LDCT	1,303	1,930
Radiography/no screening	1,395	1,986
Mortality reduction absolute	92	56
Screen detected Lung Cancer:		
Proportion of all detected cancer, %	61.2	67.9
Stage I, %	63.0	59.6
Stage II, %	7.2	8.3
Stage III, %	17.0	19.5
Stage IV, %	12.8	12.6
Small-cell carcinoma, %	7.6	5.4
Large-cell carcinoma, %	4.3	2.8
Squamous-cell carcinoma, %	21.1	23.2
Adenocarcinoma, %	39.9	50.0
Adenocarcinoma *in situ*, %	14.7	18.6
Non-small-cell carcinoma or other, %	11.6	n/a
Carcinoid, %	0.8	n/a

* for comparison purposes. The model simulates a follow-up over a lifetime course.

References

1 Scheidt-Nave C, Du Y, Knopf H, et al. Verbreitung von Fettstoffwechselstörungen bei Erwachsenen in Deutschland. *Bundesgesundheitsbl.* 2013; **56:** 661–67. doi:10.1007/s00103-013-1670-0.

2 Statistisches Bundesamt. Ergebnisse auf Grundlage des Zensus 2011. Wiesbaden, 2016.

3 Woloshin S, Schwartz LM, Welch HG. The risk of death by age, sex, and smoking status in the United States: putting health risks in context. *Journal of the National Cancer Institute* 2008; **100:** 845–53. doi:10.1093/jnci/djn124.

4 Moolgavkar SH, Luebeck G. Two-Event Model for Carcinogenesis: Biological, Mathematical, and Statistical Considerations. *Risk Analysis* 1990; **10:** 323–41. doi:10.1111/j.1539-6924.1990.tb01053.x.

5 McMahon PM, Kong CY, Johnson BE, et al. Chapter 9: The MGH-HMS Lung Cancer Policy Model: Tobacco Control Versus Screening. *Risk Analysis* 2012; **32:** S117-S124. doi:10.1111/j.1539-6924.2011.01652.x.

6 Lung Cancer: Current Diagnosis and Treatment.

7 Erasmus University Medical Center. MISCAN-Lung (Erasmus) MIcrosimulation SCreening Analysis (MISCAN) Lung Model. CISNET_ModelProfile_LUNG_ERASMUS_001_01132012_83607.pdf (accessed Jul 28, 2016).

8 Chrysanthopoulou AS. MIcrosimulation Lung Cancer (MILC) model, Package 'MILC'. https://cran.r-project.org/web/packages/MILC/MILC.pdf.

9 Hazelton WD, Clements MS, Moolgavkar SH. Multistage carcinogenesis and lung cancer mortality in three cohorts. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2005; **14:** 1171–81. doi:10.1158/1055-9965.EPI-04-0756.

10 Zentrum für Krebsregister. Lungenkrebs (Bronchialkarzinom). http://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Lungenkrebs/lungenkrebs_node.html (accessed May 12, 2016).

11 Eberle A, Jansen L, Castro F, et al. Lung cancer survival in Germany: A population-based analysis of 132,612 lung cancer patients. *Lung Cancer* 2015; **90:** 528–33. doi:10.1016/j.lungcan.2015.10.007.

12 Horeweg N, Scholten ET, de Jong, Pim A, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *The Lancet Oncology* 2014; **15:** 1342–50. doi:10.1016/S1470-2045(14)70387-0.

13 Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *The New England journal of medicine* 2011; **365:** 395–409. doi:10.1056/NEJMoa1102873.

14 Kvale PA, Johnson CC, Tammemagi M, et al. Interval lung cancers not detected on screening chest X-rays: How are they different? *Lung cancer (Amsterdam, Netherlands)* 2014; **86:** 41–46. doi:10.1016/j.lungcan.2014.07.013.

15 Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012; **307:** 2418–29. doi:10.1001/jama.2012.5521.

16 McMahon PM, Kong CY, Bouzan C, et al. Cost-Effectiveness of Computed Tomography Screening for Lung Cancer in the United States. *Journal of Thoracic Oncology* 2011; **6:** 1841–48. doi:10.1097/JTO.0b013e31822e59b3.

17 Yeow K-M, Su I-H, Pan K-T, et al. Risk Factors of Pneumothorax and Bleeding. *Chest* 2004; **126:** 748–54. doi:10.1378/chest.126.3.748.

18 Soetaert K, Petzoldt T. Inverse Modelling, Sensitivity and Monte Carlo Analysis in R Using Package FME. *J. Stat. Soft.* 2010; **33. doi:**10.18637/jss.v033.i03.

19 Diederich S, Wormanns D, Semik M, et al. Screening for Early Lung Cancer with Low-Dose Spiral CT: Prevalence in 817 Asymptomatic Smokers1. *Radiology* 2002; **222:** 773–81. doi:10.1148/radiol.2223010490.

20 National Association of Statutory Health Insurance Physicians. Uniform Value Scale. http://www.kbv.de/html/ebm.php (accessed Jul 27, 2016).

21 German Institute for the Hospital Remuneration System (InEK). G-DRG catalog. http://www.g-drg.de (accessed Jul 27, 2016).

22 Geraghty PR, Kee ST, McFarlane G, Razavi MK, Sze DY, Dake MD. CT-guided Transthoracic Needle Aspiration Biopsy of Pulmonary Nodules: Needle Size and Pneumothorax Rate1. *Radiology* 2003; **229:** 475–81. doi:10.1148/radiol.2291020499.

23 McGuire A, Martin M, Lenz C, Sollano JA. Treatment cost of non-small cell lung cancer in three European countries: comparisons across France, Germany, and England using administrative databases. *Journal of medical economics* 2015; **18:** 525–32. doi:10.3111/13696998.2015.1032974.

24 Department of Health. The likely impact of earlier diagnosis of cancer on costs and benefits to the NHS. http://www.dh.gov.uk/publications (accessed Aug 17, 2016).

25 Buckland D. New drug treatments for cancer. What the future holds. *Prescriber* 2016; **27:** 17–21. doi:10.1002/psb.1425.
26 Schremser K, Rogowski WH, Adler-Reichel S, Tufman ALH, Huber RM, Stollenwerk B. Cost-Effectiveness of an Individualized First-Line Treatment Strategy Offering Erlotinib Based on EGFR Mutation Testing in Advanced Lung Adenocarcinoma Patients in Germany. *PharmacoEconomics* 2015; **33:** 1215–28. doi:10.1007/s40273-015-0305-8.

Article 7

Pneumococcal disease in adults: a health economics evaluation of various vaccination scenarios in Germany

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Robert Koch-Institute

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Pneumococcal Disease in Adults:

a health economics evaluation of various vaccination scenarios in Germany

- Final Report -

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Conflict of interest statement:

Alexander Kuhlmann	There is no conflict of interest.
Marina Treskova	There is no conflict of interest.
J.-Matthias Graf von der Schulenburg	There is no conflict of interest.

Contents

Abstract

Background: Pneumococci (Pnc) are among the main causes of infectious disease-related mortality and morbidity, especially in the elderly. Two Pnc vaccines are available to prevent pneumococcal disease in adults: a 13-valent conjugate vaccine (PCV13) and a 23-valent polysaccharide vaccine (PPSV23) that protects against 13 and 23 of the 94 Pnc serotypes, respectively. The Standing Committee on Vaccination (STIKO) recommends PCV vaccination for infants and standard vaccination (currently with PPSV23) for people over 60. The aim of the study is to evaluate a variety of vaccination scenarios in adults aged 60 and over in the German healthcare context.

Methods: Asymptomatically colonized children are the main pathogen reservoir for Pnc. To illustrate the impact of infant vaccination on Pnc epidemiology, a dynamic transmission model was developed that forecasts the future incidence and serotype mix in Pnc cases in the over-60 age group. Replacement effects were simulated by grouping the serotypes (in accordance with the vaccines) into five groups that compete with each other in colonization. The primary outcome of the model is additional cost per QALY gained. Clinical, epidemiological and health economics parameters are based on German primary data or German and international studies. Parameter uncertainty was tested in sensitivity and scenario analyses.

Results: Sequential vaccination (PCV13 + PPSV23) prevented the largest number of Pnc infections and deaths in all the scenarios tested. In contrast, PPSV23 is considerably more efficient in most scenarios on the number needed to vaccinate in order to prevent one Pnc infection or one death. Furthermore, use of PPSV23 on its own is associated with substantially lower cost. PPSV23 is more economical and mostly more effective than vaccination with PCV13 on its own (exception: PPSV23 is not effective against noninvasive Pnc pneumonia and PCV13 is just as effective against serotype 3 as against the other PCV13 serotypes, whereas PPSV23 is only half as effective against serotype 3 as against the other PPSV23 serotypes). In all the scenarios tested, revaccination is more effective than single vaccination on the number of prevented infections as well as being more efficient on the number needed to vaccinate. The most effective strategy is multiple revaccination with PPSV23 every 6 years following sequential initial vaccination at age 60. However, in all the scenarios tested, this strategy is economically inferior to multiple revaccination with PPSV23 every 6 years after initial vaccination with PPSV23 at age 60.

Conclusion: For single vaccination, PPSV23 is preferable to other vaccination strategies from the point of view of efficiency. If the budget impact of multiple revaccination is acceptable, multiple revaccination with PPSV23 every 6 years after initial vaccination with PPSV23 at age 60 is the recommended strategy.

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1 Status quo of research

1.1 Pneumococcal infections

Pneumococci (Streptococcus pneumoniae, Pnc) are Gram-positive encapsulated bacteria. The polysaccharide capsule gives the pathogenic bacteria an element of protection from phagocytosis and adds to their virulence. Pneumococci are grouped into 94 capsule types known as serotypes based on the type of capsular polysaccharides involved. Manifestations of pneumococcal disease may be local. Examples include ear infections (otitis media) sinusitis and pneumonia. However, pneumococci can also cause invasive disease (IPDs) with manifestations including purulent meningitis, bacteremia and sepsis. IPD has an average lethality of approximately 10%, rising to more than 30% in high-risk groups. IPD mainly affects immunocompromised individuals, young children (immature immune system) and elderly people (immunosenescence).[1] The major reservoir of pneumococci is the nasopharynx of healthy carriers. About 50% of young children and 5-10% of adults have pneumococcal colonization of the nasopharynx.[2–4]

1.2 Public health

Pneumococci have significant public health relevance as a major cause of many serious diseases that are associated with high morbidity and mortality as well as a high cost of treatment. In Europe, for instance, pneumonia engenders annual costs to the tune of EUR 10.1 billion, EUR 5.7 billion of which goes for inpatient treatment, EUR 0.5 billion for non-hospital treatment and EUR 0.2 billion for medicines. The indirect cost due to lost labor input amounts to EUR 3.6 billion.[5]

1.3 Vaccines for immunization of adults against pneumococcal disease

Two types of Pnc vaccines are currently available which work by inducing the formation of antibodies against bacterial capsular polysaccharides. The older vaccine is a purely polysaccharide vaccine containing the purified capsular polysaccharide antigens of 23 of the 94 known Pnc serotypes (PPSV23). In Pnc conjugate vaccines (PCVs), the capsular polysaccharides are coupled – or conjugated – to a highly immunogenic protein (e.g., diphtheria toxin). Conjugation generates an additional T cell response compared with pure polysaccharide vaccines, which in turn results in the formation of memory cells, changes in antibody response and avidity maturation. The mucosal immunity conferred by the conjugate vaccine results in a reduction in the serotypes covered by the vaccine in asymptomatic carriers. If the immunization rate in a population is high enough, the serotypes covered by the vaccine can be reduced in the overall population as a result of indirect herd effects.

At present, immunization with PPSV23 is the standard-of-care vaccination schedule for over-60s recommended by the Standing Committee on Vaccination (STIKO).[6–8] In the presence of certain underlying diseases, STIKO says that immunization can take place either with PPSV23, a 13-valent Pnc conjugate vaccine (PCV13), or both vaccines.

In addition, revaccination every five years in individuals with congenital or acquired immunodeficiency or immunosuppression or chronic kidney disease/nephrotic syndrome is under consideration.[6–8]

PCV13 has been approved in Germany since 2009 for children and since the end of 2011 for adults over 50 and superseded the 7-valent Pnc conjugate vaccine (PCV7) for infant vaccination at the start of 2010.

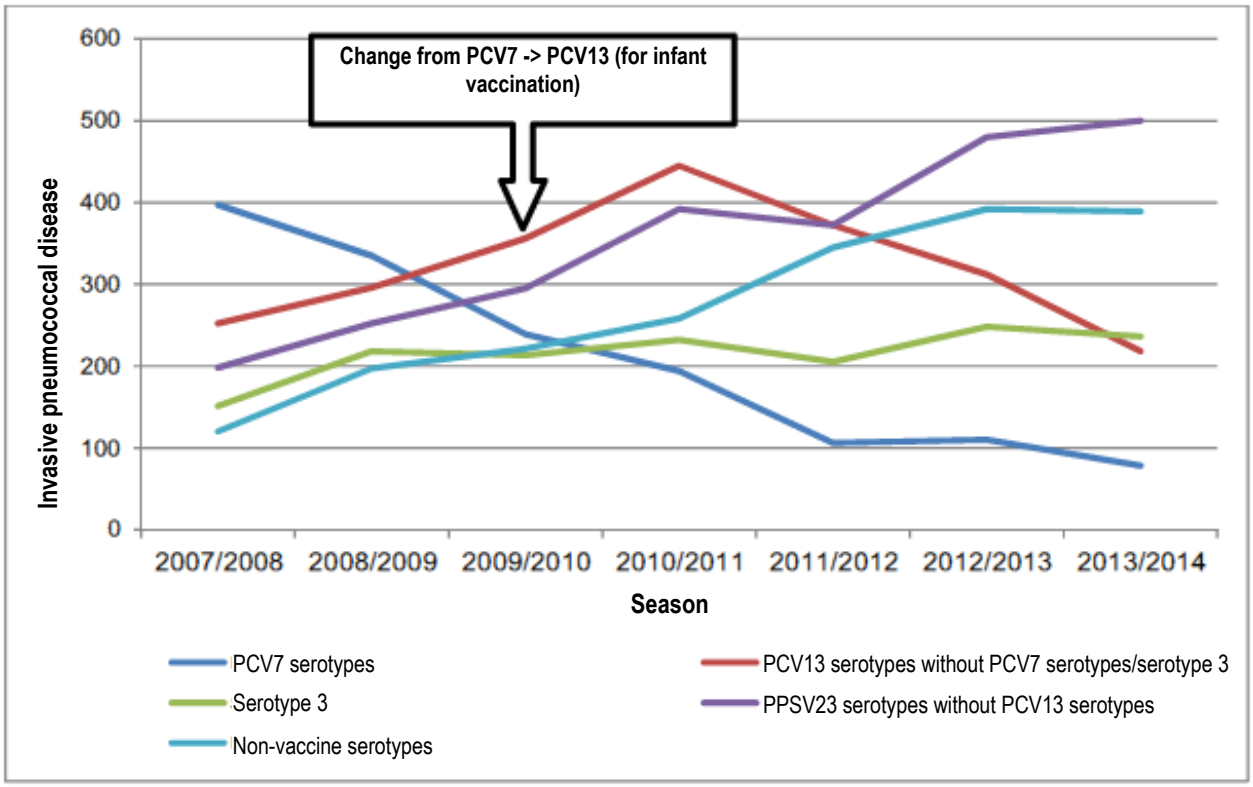
1.4 Impact of universal infant vaccination with conjugate vaccines on the epidemiology of pneumococcal infections in adults

The implementation of a universal vaccination program to vaccinate infants with PCV7 has led in many countries to a major decline in the incidence of invasive and noninvasive Pnc infections attributable to vaccine serotypes in (unvaccinated) adults.[9–13] Conversely, epidemiological data also showed a definite increase in diseases attributable to non-vaccine serotypes in the same period (in some cases with a 1-2 year delay).[14] Reduction of the PCV7 vaccine serotypes created an ecological niche that non-vaccine serotypes were able to occupy (serotype replacement). Both indirect herd effects and replacement effects have been observed in invasive pneumococcal diseases in Germany.[15, 16]

PCV13 includes one of the main replacement serotypes to date (19A) along with another five serotypes. Apart from a further reduction in PCV7 serotypes, the switch from PCV7 to PCV13 for infant immunization also produced indirect herd effects in invasive and noninvasive Pnc infections attributable to the other vaccine serotypes, while replacement effects of non-vaccine serotypes persisted.[17–21]

Germany too has seen indirect herd effects in vaccine serotypes and sustained replacement effects by non-vaccine IPD serotypes following the switch from PCV7 to PCV13.[22, 23] In contrast to the other PCV13 serotypes, a significant reduction in case numbers has not been observed to date for serotype 3 in adults (see Fig. 1). However, nor are there indications of a definite increase (such as observed for non-PCV serotypes) in serotype 3 following the change to PCV13; instead, case numbers seem to have plateaued.

Figure 1: Invasive pneumococcal disease trends in the 60+ population



Source: van der Linden et al. 2015[22]

Some western European countries are also seeing signs of persistence of serotype 3 in adults, but other western European studies are observing a definite decline.[19]

Recent studies of PCV13 also diverge in their presentation of PCV13's efficacy against serotype 3. While two studies [24, 25] point to reduced or no efficacy of the conjugate vaccine, the CAPITA study provides no indications of reduced effectiveness against serotype 3 in noninvasive Pnc pneumonia.[26] The evidence on PPSV23's efficacy against serotype 3 is similarly inconclusive.[27]

1.5 Health economics evaluation

Various health economics models investigating the cost effectiveness of Pnc vaccinations for adult immunization already exist on an international level. A systematic review [28] identified 11 studies that compared various PPSV23 vaccination programs with no vaccination. The polysaccharide vaccine was found to be cost effective in most studies. Some even identified a cost-saving effect. More recent studies endorse the cost effectiveness of PPSV23 vaccination programs versus no vaccination.[29–34]

A systematic review of PCV13 vaccination programs in adults [35] identified 10 studies. Four of them [36–39] compared PCV13 with no vaccination and six [32, 40–44] compared PCV13 with PPSV23. Three [37–39] of the four studies showed the evaluated PCV13 vaccination programs to be cost effective compared with no vaccination. PCV13 vaccination programs were cost effective compared with PPSV23 in all six studies [32, 40–44].

Another four studies comparing PCV13 are available, three of which compared PCV13 with PPSV23[29, 45, 46] and one with no vaccination [47]. In two of the studies, PCV13[45, 46] was cost effective versus PPSV23. One study produced the opposite result [29]. In the comparison with no vaccination, PCV13 was found to be cost effective.[47]

Two studies [33, 40] additionally analyzed sequential vaccination programs (PCV13+PPSV23). While one study concluded that sequential vaccination was not cost effective [40], the other study [33] found it to be preferable in immunosuppressed adults, also from an economic point of view.

Two models exist to date for the German healthcare context.[30, 48] One model [48] compared PPSV23 with PCV13. Vaccination with PCV13 dominated pure polysaccharide vaccination in this model. However, it needs to be borne in mind that the vaccines were evaluated in one scenario with PCV7 infant vaccination. In the other study [30], the potential indirect effects (indirect herd effects + replacement effects) of PCV13 vaccination in infants as a function of cumulative vaccination rates based on US data were projected to Germany. In this scenario, adult vaccination with PPSV23 was shown to be cost effective versus no vaccination.

Interstudy variability in outcome was high overall. There are many reasons for this.

1) Differences in the incidence and serotype mix of Pnc diseases in the countries investigated
2) Different cost structures in the countries investigated
3) Uncertain effectiveness of PPSV23 vaccination against noninvasive Pnc pneumonia
4) Uncertain effectiveness of PV13 vaccination in adults prior to publication of the results of the CAPITA study [26] (only one analysis so far [47] is based on the CAPITA results)
5) No conclusive data on long-term protection with PCV13 and PPSV23
6) Different vaccination programs in children (PCV7 vs. PCV10 vs. PCV13)
7) A precise estimation of the extent of indirect effects of PCV10 and PCV13 infant vaccination is not yet possible.

Nonetheless, the various results do indicate clear trends. If PCV infant vaccination produced just a small decline in the PCV13 serotypes not contained in PCV7 (or no decline) in the adult population, then adult vaccination with PCV13 would be cost effective or dominant versus no vaccination.[37–39, 47, 48] If at the same time PPSV23 were not effective against noninvasive Pnc pneumonia, then vaccination programs with PCV13 would also be cost effective or dominant versus PPSV23.[32, 40–46, 48]

Even if PPSV23 were effective against noninvasive Pnc pneumonia, PCV13 would still be cost effective as long as the conjugate vaccine displays significantly slower waning of efficacy.[48]

If there were a very strong decline in all PCV13 serotypes in adults (similar to the decline in PCV7 serotypes), then the cost effectiveness of PCV13 vaccination programs in the over-60 population versus no vaccination would be questionable.[36] If at the same time PPSV23 were effective against noninvasive Pnc pneumonia, then PCV13 would be dominated by PPSV23.[29] In this epidemiological scenario, PPSV23 would be cost effective versus no vaccination provided the effectiveness against noninvasive Pnc pneumonia were significant.[30]

Objectives and rationale

The previous sections (1.4 and 1.5) show that the body of evidence from studies so far is insufficient to define the optimum vaccination program for prevention of Pnc diseases in Germany in people over 60. This requires the most precise possible prediction of incidences and serotype mixes in Pnc infections in this age group. The latest data on the efficacy of the available vaccines should also feed into the analysis.

The aim of this model analysis is to provide a health economics evaluation of various scenarios for the prevention of Pnc infections in standard-of-care vaccination schedules in people over 60, in consideration of the epidemiological impact of infant vaccination and the specific epidemiology of serotype 3. The evaluation starts at the beginning of 2016. The effects of adult vaccination are followed in immunized individuals until the end of their lives.

The following vaccination strategies are compared in the study:

A) No vaccination

B) Single vaccinations

- PCV13: single vaccination with PCV13 in the 2016-2030 period
- PPSV23: single vaccination with PPSV23 in the 2016-2030 period
- SEQ: sequential vaccination with one dose of PCV13 + a PPSV23 booster six months later (called sequential vaccination in the following)
- SEQ_5J: sequential vaccination in the 2016-2020 period/single vaccination with PPSV23 in the 2021-2030 period

C) Revaccinations

- PPSV23_W: initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period
- SEQ_W: sequential initial vaccination + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period
- SEQ_5J_W: vaccination strategy SEQ_5J + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

Answers to the following questions are sought:

- What are the long-term epidemiological effects of the vaccination programs (incidence, disease-related deaths)?
- How many vaccinations are required to prevent one case/death, i.e., what is the "number needed to vaccinate" (NNV)?
- How cost effective are the vaccination strategies?
- What are the effects of initial vaccination age on outcomes?
- What are the effects of revaccination frequency on outcomes?

2 Methods

2.1 Selection of model type, model structure and methodology framework

A fundamental goal of modeling is to forecast the epidemiology of Pnc infections as precisely as possible. It is therefore essential to include childhood vaccination in the model in order to address its effects on the incidence and serotype mix of Pnc infections in adults. Two empirically established epidemiological effects need to be implemented in the model in this regard (see section 1.4).

- Herd effects: The conjugate vaccine prevents the carriage and hence the transmission of vaccine serotypes, such that unvaccinated individuals also benefit from indirect protection.
- Replacement effects: The replacement of vaccine serotypes by the conjugate vaccine creates an ecological niche that is penetrated by non-vaccine serotypes, resulting in an increase in carriage prevalence of these serotypes.

A mathematical model on the basis of differential equations was developed. The model covers five groups of Pnc serotypes that compete with each other to colonize the host.

- GS1: 4, 6B, 9V, 14, 18C, 19F, 23F (PCV7)
- GS2: 1, 5, 6A, 7F, 19A (PCV13/not PCV7 without serotype 3)
- GS3: 3
- GS4: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F (PPSV23/not PCV13)
- GS5: other serotypes

The model includes 16 possible carriage states:

A) No carriage

B) Carriers of one group of serotypes
   - SC1: GS1carriers
   - SC2: GS2 carriers
   - SC3: GS3 carriers
   - SC4: GS4 carriers
   - SC5: GS5 carriers

C) Carriers of two different groups of serotypes
   - DC12: GS1+GS2 carriers
   - DC13: GS1+GS3 carriers
   - DC14: GS1+GS4 carriers
   - DC15: GS1+GS5 carriers

- DC23: GS2+GS3 carriers
- DC24: GS2+GS4 carriers
- DC25: GS2+GS5 carriers
- DC34: GS3+GS4 carriers
- DC35: GS3+GS5 carriers
- DC45: GS4+GS5 carriers

The model is divided into 400 age groups (0, 3 months, 6 months, …, 99 years and 9 months). Three Pnc diseases are addressed:

- Invasive Pnc diseases (IPD: e.g., sepsis, meningitis)
- Hospitalized community-acquired noninvasive Pnc pneumonia (Pnc CAPin)
- Community-treated community-acquired noninvasive PNc pneumonia (Pnc CAPout)

Figure 2: Phases of the epidemiological submodel

Pre-childhood vaccination steady state (burn-in)	Childhood vaccination	Evaluation of adult vaccination
		No adult vaccination
		PCV13
Steady state (without vaccination)	Infant vaccination PCV7/PCV13	PPSV23
		SEQ/SEQ_5J
		PPSV23_W
		SEQ_W/SEQ_W_5J

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one dose of PCV13 + PPSV23 booster six months later; **SEQ_5J:** sequential vaccination in the 2016-2020 period/single vaccination with PPSV23 in the 2021-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** vaccination strategy SEQ_5J + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

The model comprises an epidemiological, a demographic and a health economics submodel. The epidemiological submodel forms the core of the model and simulates pneumococcal transmission in the population. It is made up of three phases (see Figure 2):

- Burn-in: The burn-in phase simulates pneumococcal transmission over a 25-year period. The aim is to generate a steady state prior to universal introduction of the conjugate vaccine for childhood vaccination as no longitudinal data are available on the incidence of IPD in Germany prior to the introduction of childhood vaccination.
- Childhood vaccination: The second phase simulates the effects of childhood vaccination between 2004 and 2015:
    - 2004-2009 childhood vaccination with PCV7 (vaccination recommendation for PCV7 in August 2006)
    - 2010-2015 childhood vaccination with PCV13
- Evaluation: The evaluation phase simulates the effects of adult vaccination in the years between 2016 and 2035 with maintenance of childhood vaccination with PCV13. The evaluation phase involves six model arms:
    - PCV13
    - PPSV23
    - SEQ/SEQ_5J
    - PPSV23_W
    - SEQ_W/SEQ_W_J
    - No adult vaccination

Each of the 400 age groups in the epidemiological submodel comprises 100,000 individuals, all of whom age by a quarter year at the same point in time. At the start of each quarter, 100,000 newborns enter the model and 100,000 99.75 year olds leave it. Mortality is not addressed in the epidemiological submodel. Given the complexity of the epidemiological model, the simplified population structure is required in order to create a steady state with a reasonable computing effort. The transmission risk is weighted with the "real-life" population structure. The outcome of the epidemiological submodel is age- and serotype-specific Pnc carrier prevalences and incidences of Pnc infection as a function of time.

The demographic submodel is designed to forecast the real-life German population structure up to the year 2070. It is based on extrapolated birth and mortality rates published by the Federal Statistical Office and given in the Human Mortality Database. The estimated size of the over-60 population is slightly above the Federal Statistical Office forecast (Variant 1 AG).

The health economics submodel links the results of the epidemiological and demographic submodel and health economics parameters. Finally, the following outcomes are calculated:

- Absolute number of Pnc cases
- Absolute number of disease-related deaths
- Overall cost of Pnc infections
- Overall cost of adult vaccination
- Years of life gained
- Quality-adjusted life years (QALY) gained

- Incremental cost effectiveness ratios
- Number of vaccinations needed per prevented case/hospitalization/disease-related death

Figure 3: Projected population trends in the over-60 population (2005-2035)

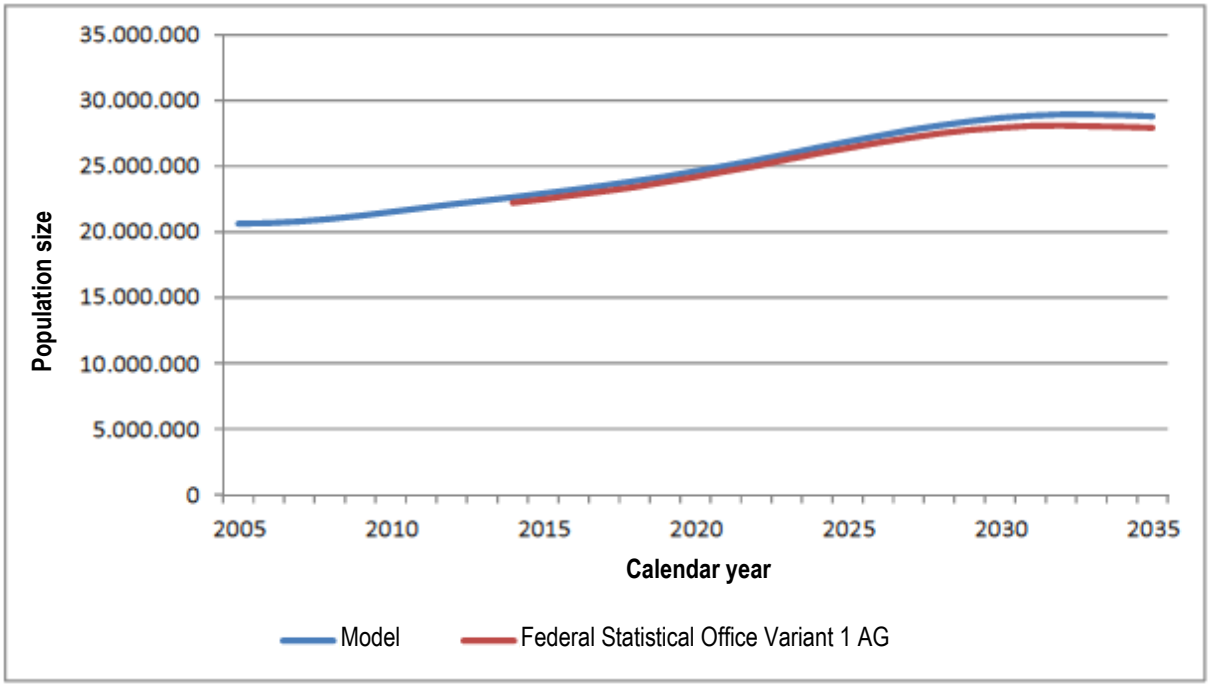
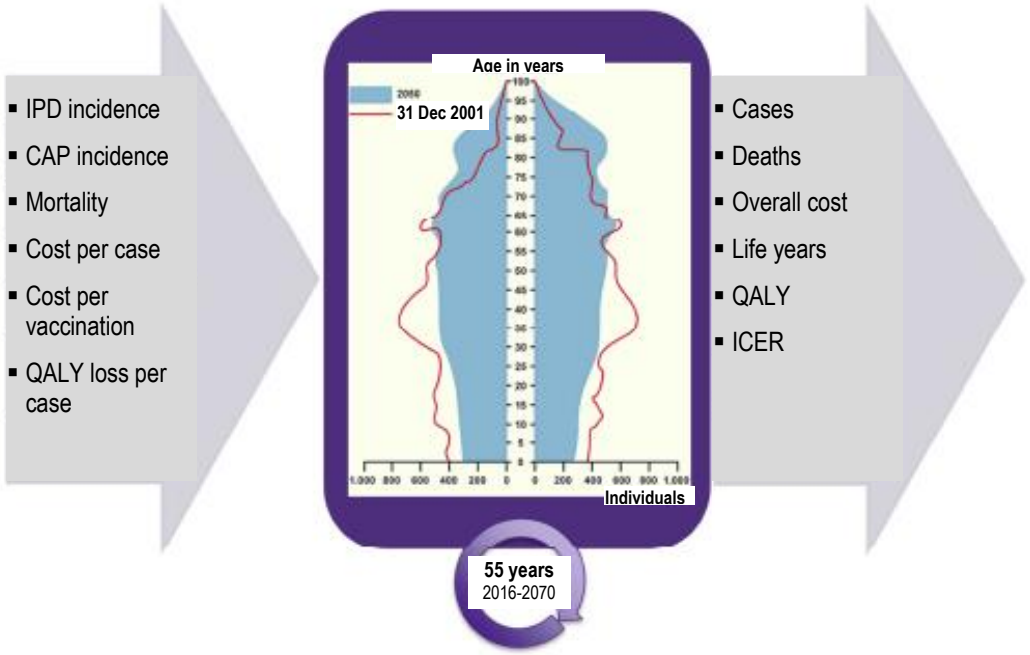


Figure 4: Demographic and health economics submodel



QALY: quality-adjusted life years; **ICER:** incremental cost effectiveness ratio

2.2 Transmission risk

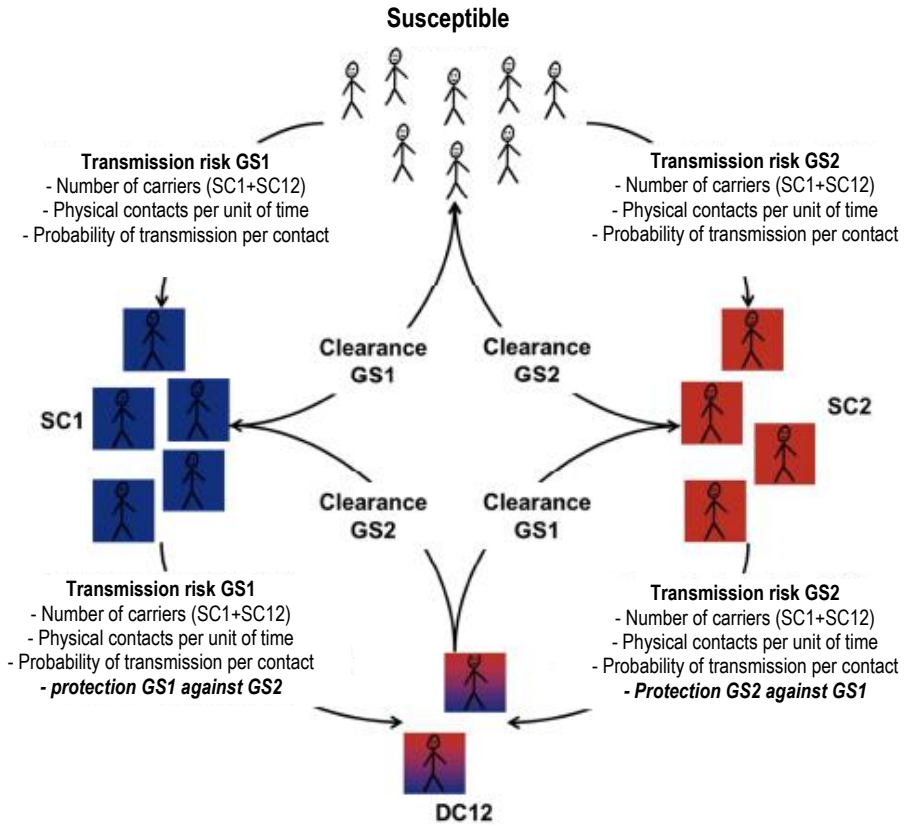
The transmission risk has four determinants:

- Number of Pnc carriers in the population
- Number of physical contacts with carriers per unit of time
- Probability of transmission per physical contact
- Existing carriage of another serotype group

The physical contact rate between two age groups and age- and serotype-dependent transmission probability per contact make up the effective contact rate. The physical contact rate is estimated on the basis of social contact data in the POLYMOD study [49]. Close contacts play a key role in pneumococcal transmission.[50, 51] Age- and serotype-dependent transmission probability per contact is estimated on the basis of epidemiological data. This is done when calibrating the models (see section 3.5).

In children protected with a Pnc conjugate vaccine, the risk of colonization by vaccine serotypes additionally depends on vaccine effectiveness against carriage as a fifth determinant. This reduces the risk of colonization.

Figure 5: Transmission risk in an unvaccinated population for two groups of serotypes [51]



GS1: Group of serotypes 1; **GS2:** Group of serotypes 2; **SC1:** GS1 carriers; **SC2:** GS2 carriers; **DC12:** Carriers of GS1 + GS2

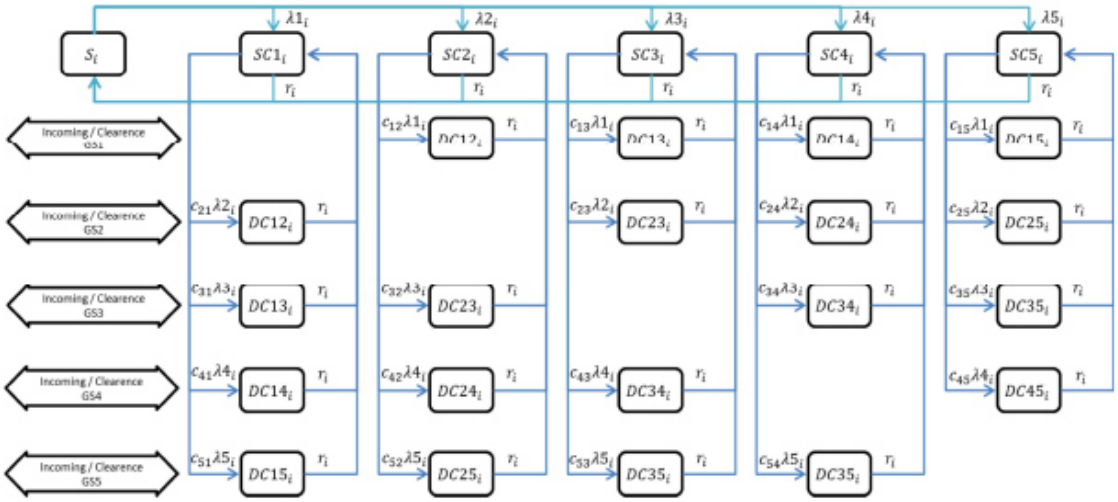
2.3 Dynamic effects

Dynamicity in the model comes from the continually changing number of Pnc carriers in the population until a steady state is obtained. Infant vaccination with a conjugate vaccine reduces the risk of colonization of the nasopharynx with vaccine serotypes. This lowers the carrier prevalence of these serotypes among vaccinated individuals. As a result, the transmission risk declines in the unvaccinated population as well.

The decline in vaccine serotypes creates an ecological niche that is occupied by non-vaccine serotypes, whose transmission risk rises as a result. To address this effect in the model, it is assumed that the five groups of serotypes compete with each other to colonize the nasopharynx. This "competition" has no effect on the duration of carriage.[52] If the nasopharynx has already been colonized by a group of serotypes, this makes it harder for another serotype group to colonize the area. The model has twenty competition parameters (c21, c31, c41, c51, c12, c32, c42, c52, c13, c23, c43, c53, c14, c24, c34, c54, c15, c25, c35, c45) that reduce the risk of dual carriage in Pnc carriers. The assumption is that colonization by no more than two different groups of serotypes is possible.

The regression of the vaccine serotypes eliminates "rivals" in the quest to colonize the nasopharynx, resulting in an increased probability of transmission of the non-vaccine serotypes.

Figure 6: Structure of the entire epidemiological submodel in the burn-in phase



S_i: Susceptible at age i; **GS1-GS5:** Serotype groups 1-5; **$SC1_i$-$SC5_i$:** GS1-GS5 carriers at age i; **$DC12_i$-$DC45_i$:** carriers of two different serotype groups at age i; **$\lambda1_i$- $\lambda5_i$:** age-dependent transmission risk of the different serotype groups; **c_{12}-c_{54}:** competition parameters; **r_i:** 1/Duration of carriage, depending on age i

2.4 Model parameters

2.4.1 Carriage

Carrier prevalence

There are no useful studies on pneumococcal carrier prevalence in Germany. International studies that might provide suitable data for modeling are very rare. Such studies would need to include a broad range of ages and should have been conducted before the introduction of childhood vaccination with PCV. If the protection the vaccine provides against infection is higher than against carriage – which is the current understanding based on the available evidence - then vaccination influences the case-carrier ratio (CCR) of the vaccine serotypes in vaccinated children. CCRs are key model parameters and should be determined in the most bias-free manner possible. Another issue is whether Pnc carrier prevalences from other countries are valid in Germany. Table 1 summarizes the main studies on pneumococcal carrier prevalence.

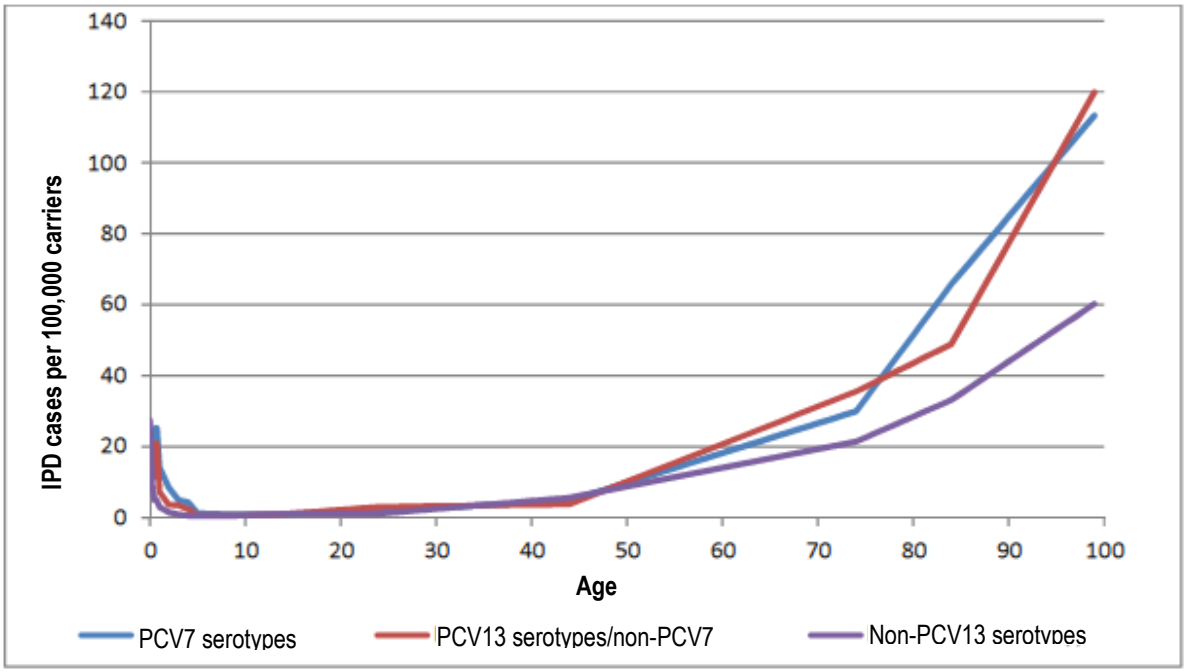
Table 1: Pnc carrier studies with a broad age range

Authors	Title	Country	Period	Population	Description
Hussain et al 2005[3]	A longitudinal household study of Streptococcus pneumonia nasopharyngeal carriage in a UK setting	UK	2001-2002	Children + adults	121 families (489 participants) over 10 months, 3752 samples; longitudinal
Leino et al 2008[4]	Clustering of serotypes in a longitudinal study of Streptococcus pneumoniae carriage in three day care centres	Finland	2001-2002	Children + adults	213 participants over 9 months, 1941 samples; longitudinal
Flasche et al 2011[53]	Effect of Pneumococcal Conjugate Vaccination on Serotype-Specific Carriage and Invasive Disease in England: A Cross-Sectional Study	UK	2008-2009	Children + adults	488 participants, 382 samples; cross-sectional; after introduction of childhood vaccination with PCV7
Van Hoek at al. 2014[54]	Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England	UK	2012/2013	Children + adults	683 participants, 683 samples; cross-sectional; after transition to PCV13 for childhood vaccination

Case-carrier ratio (CCR)

Brueggeman et al.[55]'s systematic analysis of Pnc carrier studies reports that the CCRs of individual Pnc serotypes are stable in geography and time. This suggests that generalizability is more likely here than with carrier prevalences. Extensive serotype-specific data on CCRs are available in Trotter et al.[56] and Flasche et al.[53], but CCRs were calculated for only two or three age groups. Melegaro et al.[51] and Choi et al.[50, 57] estimated age-stratified CCRs for serotype groups based on carrier prevalence and IPD incidence in the UK. This study uses the estimates provided by Choi et al.[57].

Figure 7: Case-carrier ratios in invasive pneumococcal disease



Authors' own calculations based on Choi et al.[57]; **IPD:** invasive pneumococcal disease

Carrier prevalence is determined from the transmission risk and duration of carriage. The latter was taken from the Högberg et al.[58] study. The assumption is that the duration of carriage depends solely on age. The age- and serotype-dependent transmission risk is estimated using German IPD incidences when calibrating the models (see section 3.5). The CCRs determine how many carriers are needed to induce the observed IPD incidences.

Table 2: Duration of Pnc carriage according to Högberg et al.[58]

Age	<1 year	1-2 years	3-4 years	5-17 years	>18 years
Duration of Pnc carriage	74 days	47 days	34 days	26 days	25 days

2.4.2 Pneumococcal infections

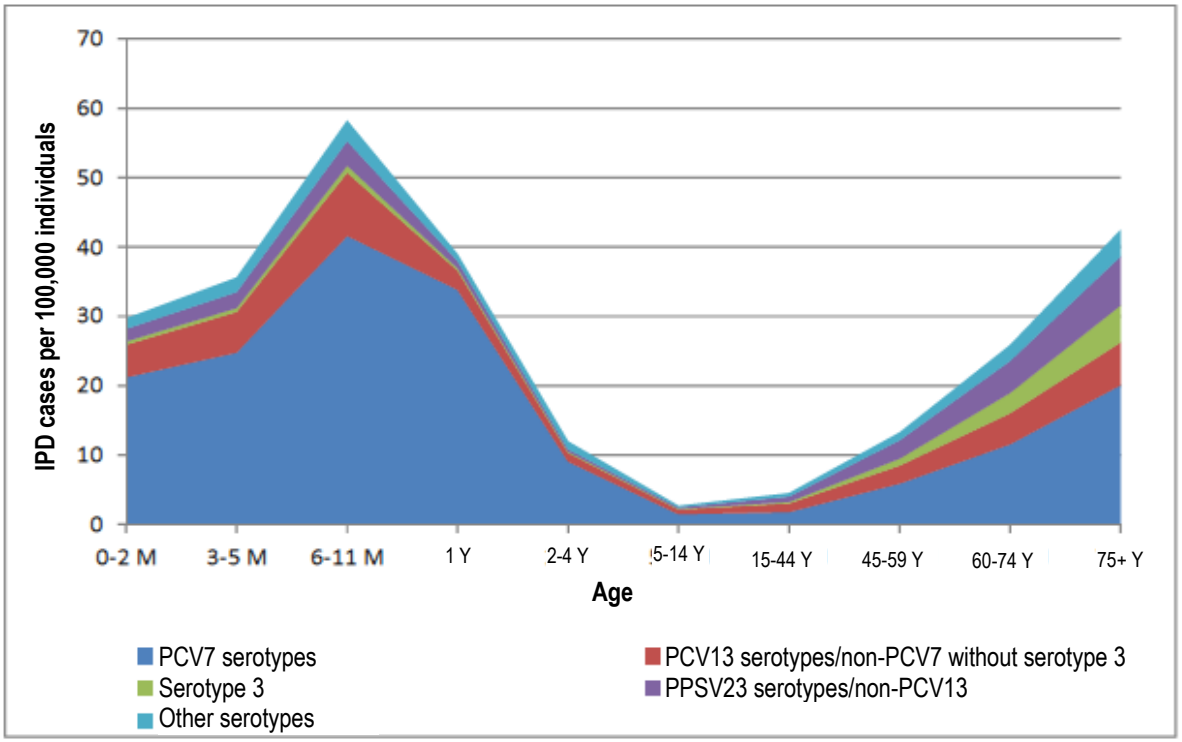
Invasive Pnc disease

The IPD incidence in children in Germany is calculated using the capture-recapture method. The data are from the two surveillance systems ESPED and Pneumoweb. Incidence data in the age groups under 2, 2 to 4 and 5-15 years of age are available for the 1997-2001 period and the period from 2007 to 2012.[23, 59] To obtain incidences for the relevant serotype groups, incidence data and the corresponding age-specific serotype distributions were linked.

Serotyping is conducted by the National Reference Center for streptococci, which provided the relevant data. Estimates of the incidence in adults are available only from a cross-sectional study in North Rhine-Westphalia[60] for the 2001-2003 period. Apart from this, only serotype distributions are known.

IPD incidences were adjusted to compensate for underestimation of case numbers due to the practice of collecting blood cultures in community-acquired pneumonia.[60]

Figure 8: Adjusted IPD incidence in the 1997-2003 period



Authors' own calculations based on Kries et al.[59], Reinert et al.[60] and National Reference Center for Streptococci; **IPD:** invasive pneumococcal disease

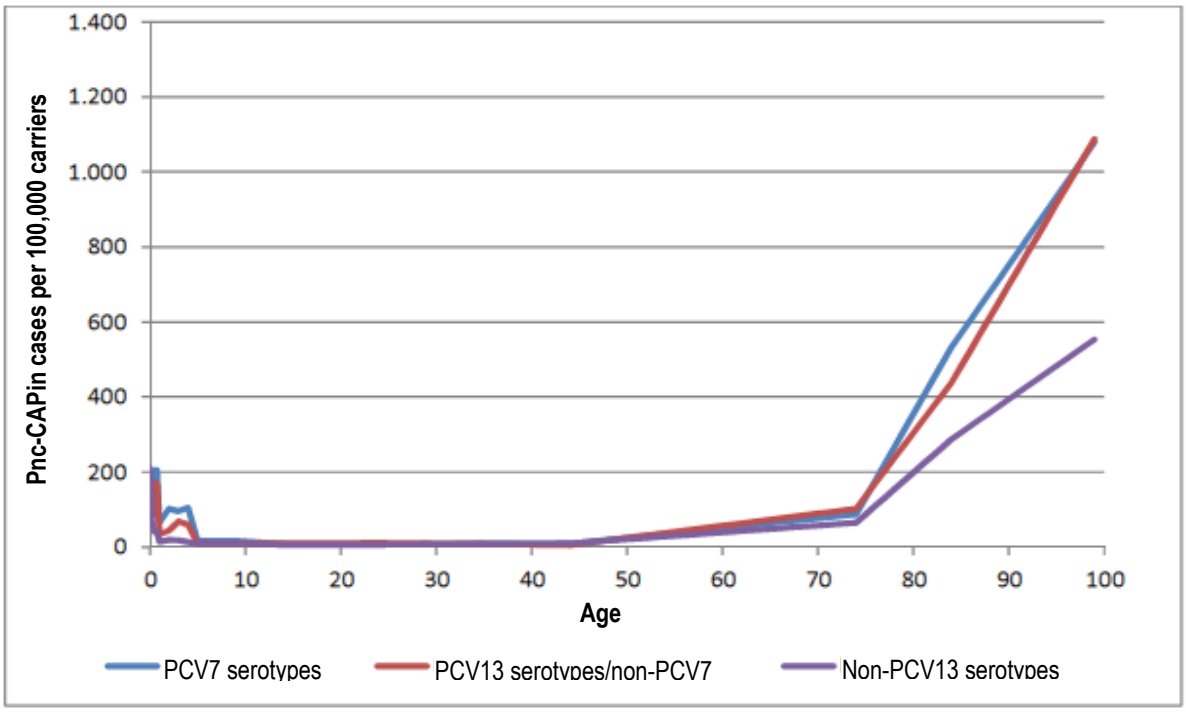
Noninvasive community-acquired pneumonia

Age-stratified Pnc-CAPin and Pnc-CAPout incidences were calculated on the basis of case numbers and prescription volumes for ICD-10 codes J12-J18 in the Federal Health Report[61] and IMS Health[62]. The assumption was that 20% of all CAP cases were caused by pneumococci [26, 63] and that the serotype mix in Pnc-CAP is similar to that in IPD.

The age- and serotype-related CCRs for noninvasive pneumonias were calculated using the following formula:

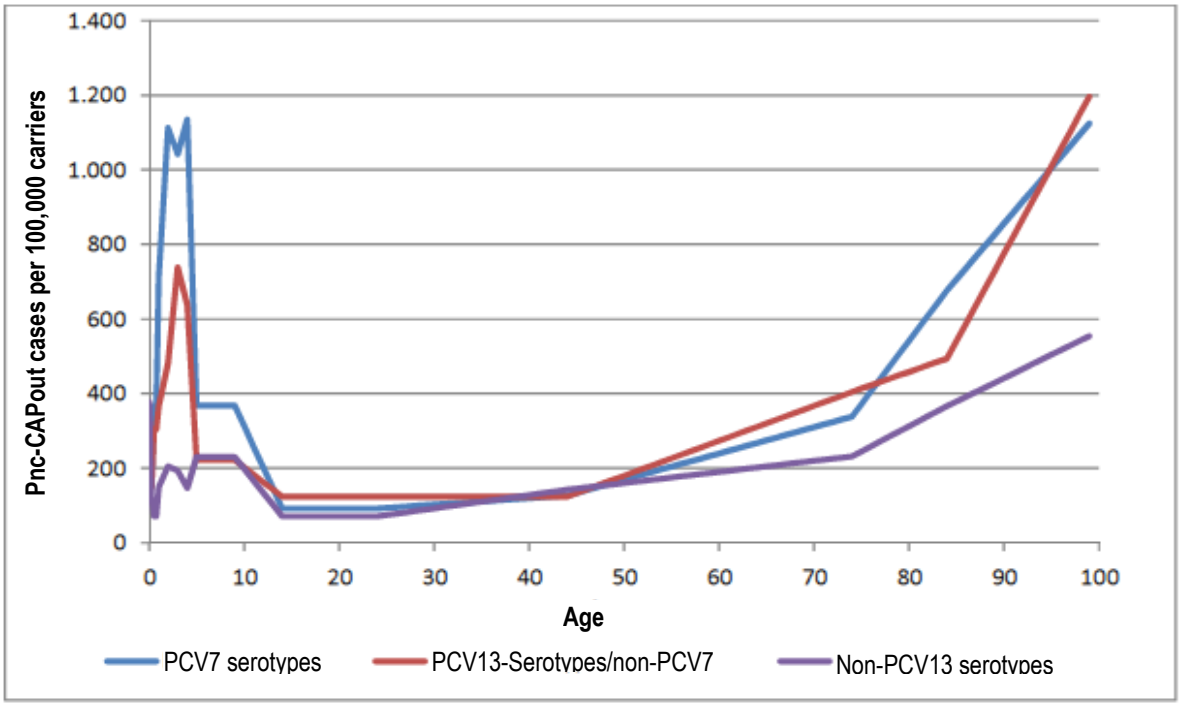
$$CAP\_CCR = IPD\_CCR * (CAP\_Incidence)/(IPD\_Incidence)$$

Figure 9: Case-carrier ratios for hospitalized Pnc- CAP (20% of all CAP cases)



Authors' own calculations based on Federal Health Report [61], adjusted IPD incidence, IPD case-carrier ratios; **Pnc-CAPin:** hospitalized noninvasive Pnc pneumonia

Figure 10: Case-carrier ratios for community-treated Pnc-CAP (20% of all CAP cases)



Authors' own calculations based on IMS Health[62], adjusted IPD incidence, IPD case-carrier ratios; **Pnc-CAPout:** community-treated noninvasive Pnc pneumonia

Lethality

Pnc infection lethality is shown in Table 3.

Table 3: Lethality in Pnc infections

Age	IPD GS1	IPD GS2	IPD GS3	IPD GS4	Pnc-CAPin	Pnc-CAPout
<1 year	3.15%	2.94%	3.11%	3.55%	0.15%	0.00%
1-4 years	3.15%	2.94%	3.11%	3.55%	0.09%	0.00%
5-14 years	10.99%	9.40%	14.69%	13.13%	0.26%	0.00%
15-24 years	10.99%	9.40%	14.69%	13.13%	0.84%	0.00%
25-44 years	10.99%	9.40%	14.69%	13.13%	1.42%	0.00%
45-64 years	10.99%	9.40%	14.69%	13.13%	6.02%	0.40%
65-74 years	32.48%	29.33%	28.56%	31.51%	9.99%	0.40%
75-84 years	32.48%	29.33%	28.56%	31.51%	14.23%	0.40%
85+ years	32.48%	29.33%	28.56%	31.51%	20.13%	0.40%
Source	van Hoek 2012[64], NRC for Streptococci				Federal Statistical Office [61]	CAPNETZ

GS1: PCV7 serotypes**; GS2:** PCV13 serotypes/non-PCV7 without serotype 3; **GS3:** serotype 3; **GS4:** PPSV23 serotypes/non-PCV13; **GS5:** non-vaccine serotypes; **IPD:** invasive pneumococcal disease; **Pnc-CAPin:** hospitalized noninvasive Pnc pneumonia; **Pnc-CAPout:** community-treated noninvasive Pnc pneumonia; **NRC:** National Reference Center

2.4.3 Vaccination

Vaccination rates

In August 2006 the Standing Committee on Vaccination at the Robert Koch Institute recommended universal vaccination of infants with PCV7 in accordance with the 3+1 vaccination schedule. The vaccination rate soared in consequence. In January 2010, PCV7 was superseded by PCV13. Age-stratified vaccination rates in children were calculated quarterly on the basis of data provided by statutory health insurance physician associations (KV data). The records go back to January 2004. Infants who had received at least two doses of PCV vaccine were considered vaccinated. A vaccination rate of 30% was assumed for adult vaccination.[65]

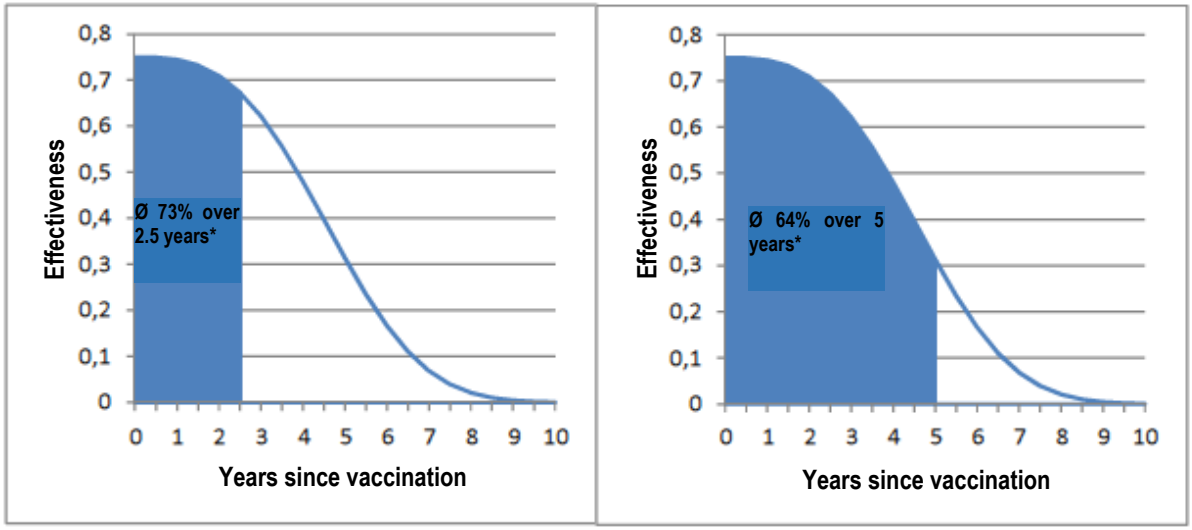
Effectiveness

It was assumed that the vaccinations were effective only against vaccine serotypes (VTs) (and not against vaccine-related serotypes). It was also assumed that the protection conferred by vaccination declined continually over time (an effect called waning). As the effects reported in the studies relate to a specific period of time, the values were extrapolated back to the time of vaccination, assuming a waning rate.

A fixed waning rate was imputed for pediatric vaccination that corresponds to the inverse of the expected duration of immunity. Effectiveness (at the time of vaccination) against vaccine serotype carriage and the expected duration of PCV immunity in children were estimated when calibrating the models (see section 3.5). It was assumed that pediatric vaccination against VT-IPD has 100% effectiveness at the time of vaccination.

A time-dependent waning rate was imputed in adult vaccination, with waning of immunity in just a few individuals during the first years after vaccination. After this period, however, the number of protected individuals declines rapidly. A time-dependent rate could not be used for infant vaccination because the model lacks the necessary memory with regard to the exact vaccination age of the infants concerned.

Figure 11: Expected anti-VT-IPD effectiveness of PPSV23 for various periods of time *



RKI meta-analysis of RCTs[66]: 73% vaccine effectiveness with an average study duration of 2.5 years

Cohort study, Ochoa-Gondar et al.[67]: 64% vaccine effectiveness with an average follow-up of 5 years

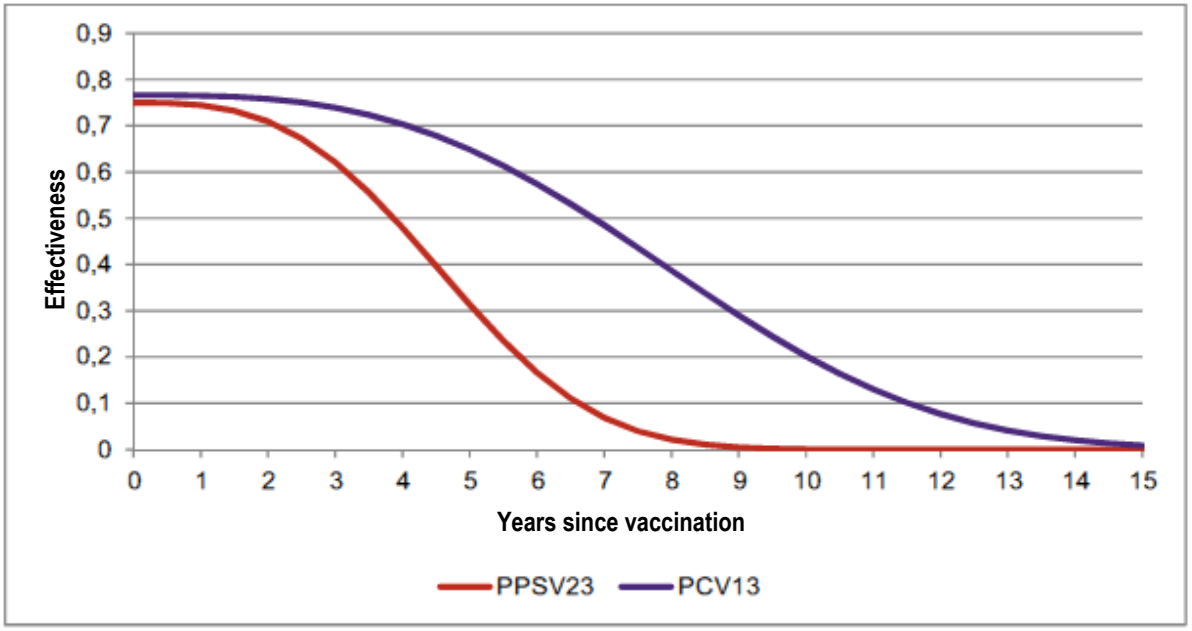
* The expected effectiveness for a specific interval of time is calculated from the area under the curve divided by the length of time.

VT-IPD: Invasive pneumococcal cases caused by vaccine serotypes

When calibrating the models, an expected duration of immunity of 8.2 years (IPD and CAP) in children was estimated for the PCV vaccine. This value is very close to the results in a study by Melegaro et al.[68]. The same duration of immunity was imputed for adult vaccination with PCV13. Effectiveness at the time of vaccination was then calculated on the basis of the results of the CAPITA study [26] and the duration of immunity. An expected duration of immunity with PPSV23 was calculated both for IPD (4.67 years) and for CAP (3.75 years). This was calculated to achieve the effectiveness levels for randomized controlled trials calculated in a meta-analysis by the Robert Koch Institute [66] and the levels seen in the non-interventional study by Ochoa-Gondar[67], taking the respective study durations into account. Figure 11 shows the trends for IPD, by way of example. Figures 12 and 13 present a comparison of the effectiveness of PCV13 and PPSV23 as a function of time.

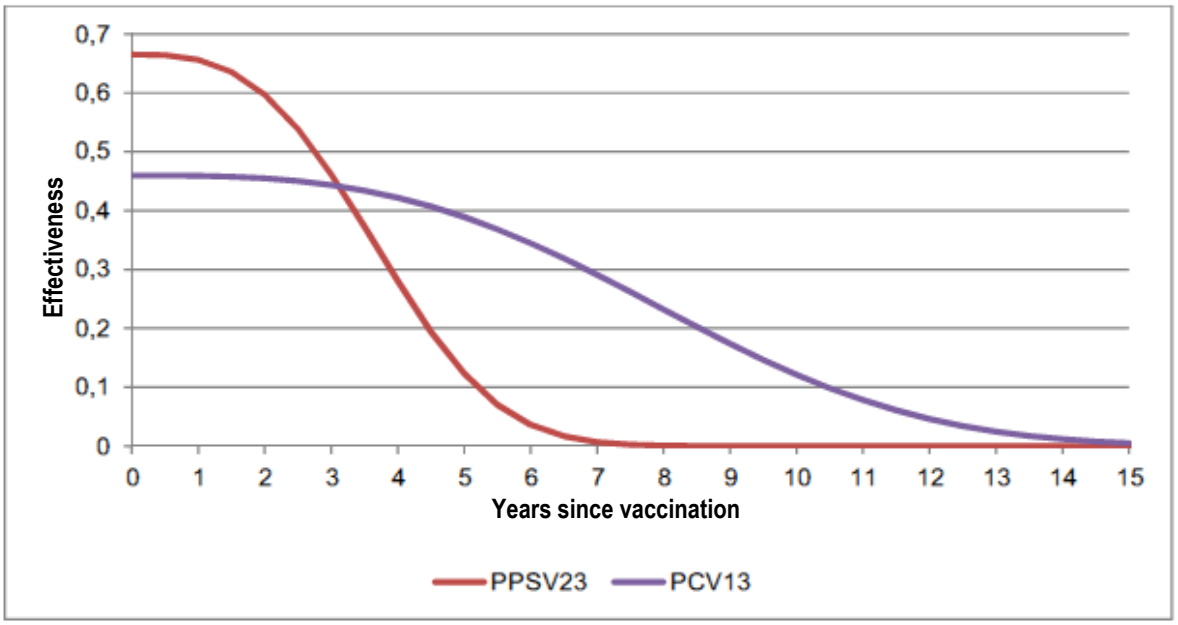
It was assumed that the efficacy of revaccination with PPSV23 declines by 0%-25% versus the initial vaccination with PPSV23.

Figure 12: Effectiveness of adult vaccination against VT-IPD



VT-IPD: Invasive pneumococcal disease caused by vaccine serotypes

Figure 13: Effectiveness of adult vaccination against VT-Pnc-CAP



VT-Pnc-CAP: Noninvasive Pnc pneumonia caused by vaccine serotypes

2.4.4 Cost

Cost was determined in accordance with German recommendations on "Evaluation of resources in the healthcare system from the perspective of the German social security system"[69] and indirect cost due to lost labor input was added.

Vaccination prices

The cost of pneumococcal vaccination is made up of the drug price and the vaccination fee. It was assumed that the insurance flat rate has fallen due and that pneumococcal vaccination coincides with other vaccinations (such as influenza vaccination). The drug prices were taken from the official German price list for prescription medicines (Lauer-Taxe[70]). Pharmacy retail prices were adjusted for pharmaceutical industry and pharmacy rebates. The result was a dose price of EUR 60.24 for PCV13 and EUR 29.08 for PPSV23. The vaccination fee was calculated as weighted average of current vaccination agreements in the federal states, resulting in a price of EUR 7.19.

Direct cost of illness

The cost of treating a Pnc case was defined as direct cost of illness. A weighted average across various G-DRG flat fees was calculated for IPD and Pnc-CAPin. The cost of treatment of a Pnc-CAPout case was determined by adding the health insurance flat fee for a primary care physician and the cost of antibiotic drug therapy. The pricing year is 2014 (2015 for PCV13 and PPSV23 prices).

Table 4: Direct cost of illness per Pnc case

Disease		Cost per case	Reference
IPD		EUR 8,581	87% weighted average T60A,C; B72B + 13% weighted average A07C-D; A09C-E; A11C,E-F; A13B-C,E-F[71]
Pnc-CAPin		EUR 3,178	95% weighted average E77B-F,I + 5% weighted average A09C-D,F; A11E,G-H; A13E,G-H[71]
Pnc-CAPout	60-<75 years:	EUR 15.90	03004 EBM 2014[72]
	75+ years:	EUR 21.27	03005 EBM 2014[72]
	Drugs:	EUR 23.91	IMS HEALTH 2009[62]

IPD: Invasive pneumococcal disease; **Pnc-CAPin:** hospitalized noninvasive Pnc pneumonia; **Pnc-CAPout:** community treated noninvasive Pnc pneumonia

Indirect cost/productivity loss

Productivity loss due to Pnc cases was calculated on the basis of the friction cost approach. Friction time was 77 days in 2014.[73] This value was used for the production loss associated with one disease-related death. In 2014, employee salary was EUR 104 per day per capita.[74] Employment rates for the age groups of 60-64, 65-74 and 75+ were 46.36%, 5.93% and 0%.[75] The average number of days off work in the 60+ age group was 39.30 per IPD case and 18.65 per CAP case.[76]

2.4.5 Quality of life

The quality of life values and losses used in the model are presented in Table 5. Age-specific values were calculated for the five serotype groups in IPD. Any late complications were discounted on the Pnc date.

Table 5: Quality of life and quality of life losses in Pnc cases

Parameters	Age group	Unit	QALY	Source
Population	<18	Year	0.879	Assumption
	18-<30		0.879	EuroQol 2004[77]
	30-<40		0.870	
	40-<50		0.833	
	50-<60		0.798	
	60-<70		0.746	
	70-<80		0.755	
	80+		0.631	
Meningitis	All	Case	-0.0232	van Hoek 2012[64] Melegaro 2004[68]
Bacteremia/sepsis	All	Case	-0.0079	
Empyema	All	Case	-0.0232	
Pnc-CAPin	All	Case	-0.0060	
Pnc-CAPout	All	Case	-0.0040	
Late complications*	All	Year	-0.2550	

*Probability of late complications of meningitis: 31.7%[78]

QALY: quality-adjusted life years; **Pnc-CAPin:** hospitalized noninvasive Pnc pneumonia; **Pnc-CAPout:** community treated noninvasive Pnc pneumonia

2.4.6 Discounting

Cost and life years gained / QALYs were discounted at a rate of 3% in accordance with IQWiG [German Institute for Quality in Health Care] recommendations in the base case analysis.[79]

2.5 Calibrating the models

50 parameters were fitted when calibrating the models. Eight age-dependent transmission probabilities per social contact were estimated for each serotype group. Six (c21, c31, c41, c51, c42, c52) of the twenty competition parameters were also calibrated (the other competition parameters were fixed at a value of 0.5) and effectiveness of the conjugate vaccination against pneumococcal carriage, expected duration of immunity and reduction of effectiveness against serotype 3 (in carriage and Pnc cases). All parameters were calibrated simultaneously with a direct optimization method. For this purpose, the sum of squared differences between the logarithmized IPD incidences and serotype distributions of the model and the logarithmized empirical data was minimized.

Both the Nelder-Mead algorithm and the Levenberg-Marquardt algorithm were used as optimization methods. As the Nelder-Mead method did not converge after 10,000 iteration steps, the results of the Levenberg-Marquardt algorithm were used.

2.6 Summary of input parameters and model assumptions

Table 6: Summary of input parameters and model assumptions in the base case

Parameter	Value	Source
Vaccination rate among seniors	30%	DEGS study
Effectiveness of PPSV23		
Against VT-Pnc-CAP	67% (0%;83%)	Calculated on the basis of the RKI meta-analysis [66]; see section 3.4.3
Against VT-IPD	75% (38%;95%)	
Immunity duration VT-IPD	4.7 years	
Immunity duration VT-Pnc-CAP	3.8 years	
against Serotype 3		Assumption: PPSV23 is only half as effective against serotype 3 as against the other vaccine serotypes (ineffective; equal effectiveness)
VT-Pnc-CAP	34% (0%;83%)	
VT-IPD	38% (0%;95%)	
Effectiveness of PPSV23 revaccination	75%-100% of initial PPSV23 vaccination	Assumption; see section 3.4.3
Effectiveness of PCV13		
against VT-Pnc-CAP	46% (15%;67%)	Calculated on the basis of the CAPITA study [26] and results of calibrating PCV childhood vaccination models; see section 3.4.3
against VT-IPD	77% (42%;93%)	
Immunity duration	8.2 years	
against serotype 3		Assumption: PCV13 is only have as effective against serotype 3 as against the other vaccine serotypes (ineffective; equal effectiveness)
VT-Pnc-CAP	23% (0%;67%)	
VT-IPD	39% (0%;93%)	
IPD incidences	The age- and serotype-specific incidences are the result of the dynamic transmission model for Pnc carriage based on infant vaccination since 2006. The model was calibrated on the basis of German data on IPD incidence [15, 23, 59] and the serotype mix [22]. See sections 3.4.2, 3.5.	
Pnc-CAP incidences	The age- and serotype-specific incidences are the result of the dynamic transmission model for Pnc carriage based on infant vaccination since 2006. Incidence rates before the introduction of PCV childhood vaccination are from the Federal Health Report [61] and IMS Health[62]. The assumption was that the serotype mix in Pnc-CAP and IPD is similar and that Pnc-CAP accounts for 20% of all CAP cases [26, 63] See section 3.4.2.	
Lethality		
IPD	2.9%-32.5%	Age- and serotype-specific data from the UK [64], adjusted to serotype mix and age structure in Germany [22]. See section 3.4.2.
Pnc-CAPin	0.2%-20.1%	Age-dependent; Federal Health Report [61]. See section 3.4.2.
Pnc-CAPout	0%-0.4%	Age-dependent; CAPNETZ. See section 3.4.2.
QALY loss per case (including deaths)		
IPD	0.51-4.04	Age- and serotype-specific data from the UK [64], adjusted to serotype mix and age structure in Germany [22]. See section 3.4.5.
CAP, hospital treated	0.28-1.27	Age-dependent. See section 3.4.5.
CAP, community treated	0.01-0.07	Age-dependent. See section 3.4.5.

Cost of illness per case		
IPD	EUR 8581	DRG browser 2012/2014[71]. See section 3.4.4.
Pnc-CAPin	EUR 3178	DRG browser 2012/2014[71]. See section 3.4.4.
Pnc-CAPout	EUR 40-45	Age-dependent; EBM Catalogue 2014[72], IMS Health[62]. See section 3.4.4.
Absence from work (per day)	EUR 104	Federal Statistical Office 2014[74]. See section 3.4.4.
Vaccine prices (per dose from a pack of 10)		
PPSV23	EUR 29.08	Lauer-Taxe [official drug price list in Germany] 15 Oct 2015[70]. See section 3.4.4.
PCV13	EUR 60.24	Lauer-Taxe 15 Oct 2015[70]. See section 3.4.4.
Vaccination fee	EUR 7.19	Average from current vaccination agreements. See section 3.4.4.
Discount	3%	IQWiG[79]. See section 3.4.6.

VT-IPD: Invasive pneumococcal disease caused by vaccine serotypes; **VT-Pnc-CAP:** Non-invasive Pnc pneumonia caused by vaccine serotypes; **Pnc-CAPin:** hospitalized noninvasive Pnc pneumonia; **Pnc-CAPout:** community-treated noninvasive Pnc pneumonia; **QALY:** quality-adjusted life years

2.7 Model analyses

Two epidemiological scenarios were calibrated:

- Scenario A: Persistence of serotype 3 at level of Pnc season 2013/2014
- Scenario B: Delayed elimination of serotype 3

In addition, four scenarios on the effectiveness of adult vaccinations were established. These explore the effectiveness of PCV13 and PPSV23 against serotype 3 and the effectiveness of PPSV23 against VT-Pnc-CAP:

- Scenario A1/B1
    - PPSV23 effective against Pnc-CAP
    - Reduced effectiveness against serotype 3 with PCV13 and PPSV23 (compared with the other vaccine serotypes)
- Scenario A2/B2
    - PPSV23 effective against Pnc-CAP
    - Reduced effectiveness against serotype 3 only with PPSV23 (compared with the other vaccine serotypes)
- Scenario A3/B3
    - PPSV23 not effective against Pnc-CAP
    - Reduced effectiveness against serotype 3 with PCV13 and PPSV23 (compared with the other vaccine serotypes)
- Scenario A4/B4
    - PPSV23 not effective against Pnc-CAP
    - Reduced effectiveness against serotype 3 only with PPSV23 (compared with the other vaccine serotypes)

Each of the eight scenarios that emerged was run with base case analysis with the most probable set of parameters and sensitivity analyses on the effectiveness of the vaccinations (lower limit; upper limit), age at initial vaccination and frequency of revaccinations. The assumptions on vaccination effectiveness in the various scenarios are outlined in Table 7. Variations of scenarios A1/B1 are highlighted in bold.

The following outcomes were calculated in each analysis:

- Absolute number of pneumococcal disease cases/disease-related deaths
- Overall cost of pneumococcal disease cases
- Overall cost of adult vaccination
- Years of life gained
- Quality-adjusted life years (QALY) gained
- Incremental cost effectiveness ratios
- Number needed to vaccinate per prevented case/hospitalization/disease-related death

Table 7: Effectiveness of adult vaccinations in the various scenarios

		Epidemiology of serotype 3		
		Persistence (at the level of the 2013/2014 Pnc season)	Delayed elimination (versus the other PCV13 serotypes)	
PPSV23 effective against Pnc-CAP	Reduced effectiveness against serotype 3 with PCV13 and PPSV23	**Scenario A1**	**Scenario B1**	
		Effectiveness PPSV23		
		against VT-Pnc-CAP	67% (0%;83%)	RKI meta-analysis[66]**
		against VT-IPD	75% (38%;95%)	
		against serotype 3		
		VT-Pnc-CAP	34% (0%;83%)*	Assumption: effectiveness against serotype 50% reduced
		VT-IPD	38% (0%;95%)*	
		Effectiveness PCV13		
		against VT-Pnc-CAP	46% (15%;67%)	CAPITA[26]**
		against VT-IPD	77% (42%;93%)	
		against serotype 3		
		VT-Pnc-CAP	23% (0%;67%)*	Assumption: effectiveness against serotype 50% reduced
		VT-IPD	39% (0%;93%)*	
	Reduced effectiveness against serotype 3 only with PPSV23	**Scenario A2**	**Scenario B2**	
		Effectiveness PPSV23		
		against VT-Pnc-CAP	67% (0%;83%)	RKI meta-analysis[66]**
		against VT-IPD	75% (38%;95%)	
		against Serotype 3		
		VT-Pnc-CAP	34% (0%;83%)*	Assumption: effectiveness against serotype 50% reduced
		VT-IPD	38% (0%;95%)*	
		Effectiveness PCV13		
		against VT-Pnc-CAP	46% (15%;67%)	CAPITA[26]**
		against VT-IPD	77% (42%;93%)	
		against Serotype 3		
		VT-Pnc-CAP	**46% (15%;67%)**	**Assumption: no reduced effectiveness against serotype 3**
		VT-IPD	**77% (42%;93%)**	
PPSV23 not effective against Pnc-CAP	Reduced effectiveness against serotype 3 with PCV13 and PPSV23	**Scenario A3**	**Scenario B3**	
		Effectiveness PPSV23		
		against VT-Pnc-CAP	**0% (0%;0%)**	**Moberley[80], Huss[81]**
		against VT-IPD	75% (38%;95%)	RKI meta-analysis[66]**
		against Serotype 3		
		VT-Pnc-CAP	**0% (0%;0%)***	Assumption: effectiveness against serotype 50% reduced
		VT-IPD	38% (0%;95%)*	
		Effectiveness PCV13		
		against VT-Pnc-CAP	46% (15%;67%)	CAPITA[26]**
		against VT-IPD	77% (42%;93%)	
		against Serotype 3		
		VT-Pnc-CAP	23% (0%;67%)*	Assumption: effectiveness against serotype 50% reduced
		VT-IPD	39% (0%;93%)*	
	Reduced effectiveness against serotype 3 only with PPSV23	**Scenario A4**	**Scenario B4**	
		Effectiveness PPSV23		
		against VT-Pnc-CAP	**0% (0%;0%)**	**Moberley[80], Huss[81]**
		against VT-IPD	75% (38%;95%)	RKI meta-analysis[66]**
		against Serotype 3		
		VT-Pnc-CAP	**0% (0%;0%)***	Assumption: Effectiveness against serotype 0% reduced
		VT-IPD	38% (0%;95%)*	
		Effectiveness PCV13		
		against VT-Pnc-CAP	46% (15%;67%)	CAPITA[26]**

		against VT-IPD	77% (42%;93%)	
		against Serotype 3		
		VT-Pnc-CAP	**46% (15%;67%)**	**Assumption: no reduced effectiveness against serotype 3**
		VT-IPD	**77% (42%;93%)**	

VT-IPD: Invasive pneumococcal disease caused by vaccine serotypes; **VT-Pnc-CAP:** Noninvasive Pnc pneumonia caused by vaccine serotypes
*In parentheses: lower limit; upper limit
** Authors' own calculations: see section 3.4.3.

3 Results

The main results of Scenario A are presented in the following, as Scenario A was assumed to be the more probable case. In Scenario B, the results for PCV13 and sequential vaccination versus vaccination with PPSV23 alone are much poorer. Detailed results of both scenarios were sent to the RKI in separate documents. A vaccination rate of 30%[65] in seniors was assumed for all scenarios.

The results for the base case are given in each case, along with the results for the upper and lower limits of vaccination effectiveness in parentheses (see section 3.7, Table 7).

3.1 Impact of pediatric vaccination on the epidemiology of pneumococci in Germany

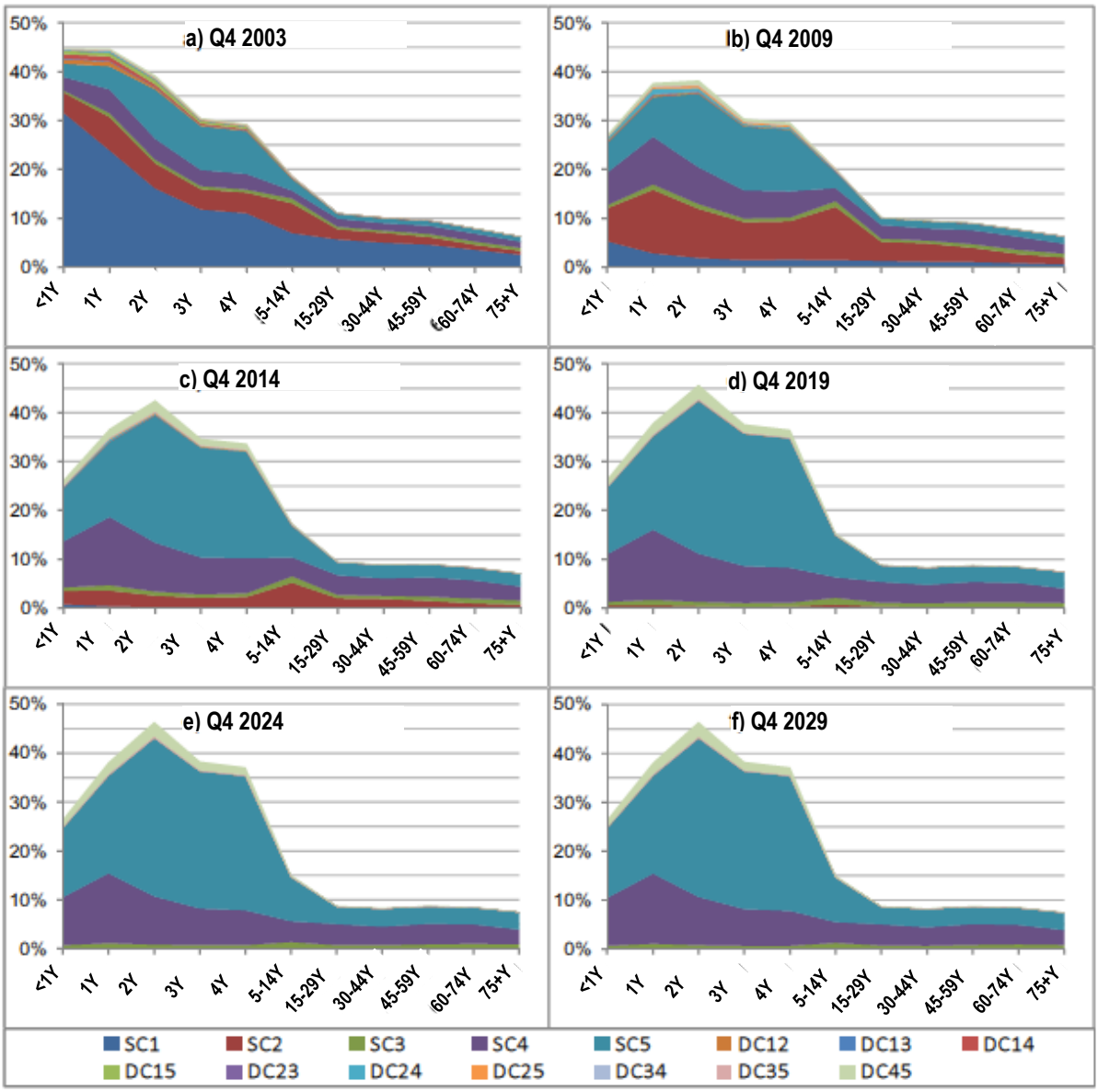
3.1.1 Impact of pediatric vaccination on pneumococcal carrier prevalence

Figure 14 shows the Pnc carrier prevalences for various age groups as a function of time as simulated by the model. Graph 14a) (4th quarter 2003) shows the steady state before the STIKO recommendation for infant vaccination with PCV7. Due to the case carrier ratios, the serotype mix in asymptomatic carriers differs from the serotype mix in invasive Pnc cases. Because of the higher case carrier ratios of PCV7 serotypes, they account for a smaller percentage of total carrier prevalence than IPD incidence (see Figures 8, 14). The percentage of non-PCV13 serotypes in overall carrier prevalence is much higher than with IPD because of the lower case carrier ratios. The difference in the invasiveness of the various serotypes is a decisive factor in determining indirect net effects of infant vaccination (indirect herd effects minus replacement infections). Even if replacement is complete on the level of carriage, lower case carrier ratios of the non-vaccine serotypes would lead to positive effects as regards Pnc infections.

Elimination of PCV7 serotypes in particular favors the spread of the additional serotypes contained in PCV13 (Fig. 14b). The introduction of pediatric vaccination with PCV13 in the 1st quarter of 2010 however then leads to a decline in the additional PCV13 serotypes (except serotype 3). The process is initially slower than with the PCV7 serotypes because the additional PCV13 serotypes have not yet achieved a new steady state at the introduction of the higher-valency conjugate vaccine and were still in the process of rising, a process favored among other things by the sustained elimination of the last remaining PCV7 serotypes.

The prevalence of serotype 3 carriers continues to increase slightly in most age groups in Scenario A between 2016-2020 (by -1.5% – 5.7% until 2020 depending on age group) because of the sustained replacement of the other PCV13 serotypes and the reduced protection conferred by the pediatric vaccination against colonization by serotype 3. The model predicts that the prevalence of serotype 3 will decline again by just under 10% by the year 2030 compared with the levels in the 4th quarter of 2019 (see Fig. 14d and 14f).

Figure 14: Predicted Pnc carrier prevalence for various age groups



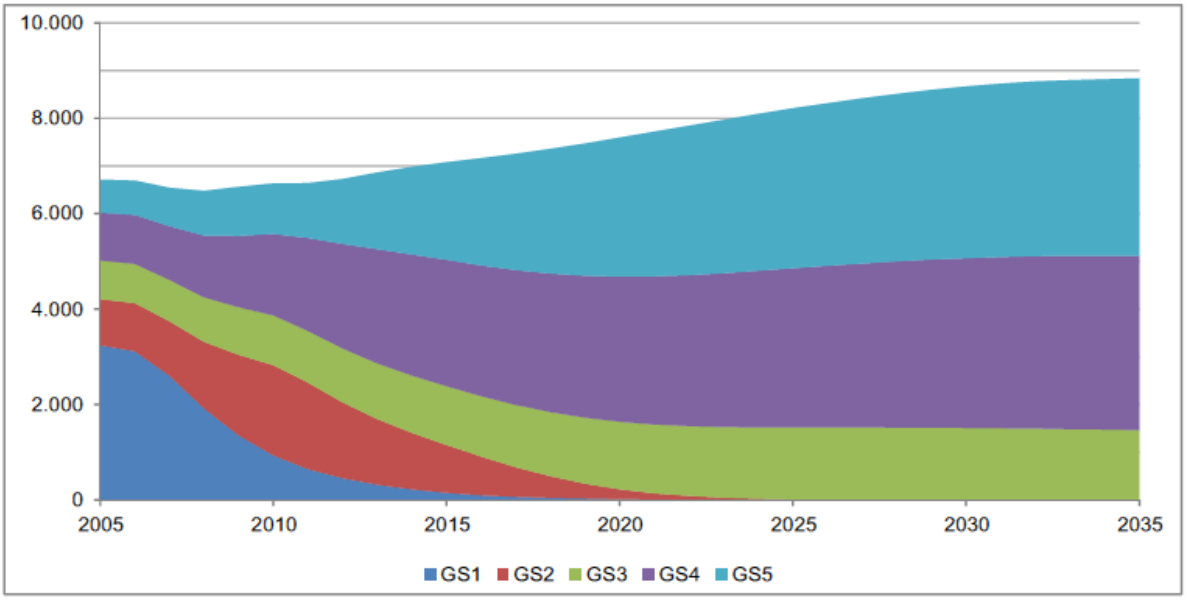
SC1: Carriers of PCV7 serotypes; **SC2:** Carriers of PCV13 serotypes without PCV7 serotypes and serotype 3; **SC3:** Carriers of serotype 3; **SC4:** Carriers of PPSV23 serotypes without PCV13 serotypes; **SC5:** Carriers of non-vaccine serotypes; **DC12-DC45:** Dual carriers of the relevant serotype groups.

3.1.2 Impact of pediatric vaccination on the incidence of invasive pneumococcal disease in adults >= 60 years of age

The impact of infant vaccination on the prevalence and serotype mix in Pnc colonizations of the nasopharynx is changing the epidemiology of Pnc infections.

The model predicts almost complete disappearance of PCV13 serotypes except serotype 3 by the year 2020. Vaccine serotypes are being replaced in part by non-PCV13 serotypes. Despite positive indirect net effects of infant vaccination, demographic effects are driving a sharp increase in IPD cases in the over-60 population (see section 3.1, Fig. 3 for demographic trends in the 60+ population). Without PCV13 pediatric vaccination, the model would predict about 25%-30% more cases by 2055.

Figure 15: Predicted number of invasive Pnc cases in the 60+ population



GS1: PCV7 serotypes; **GS2:** PCV13 serotypes without PCV7 serotypes and serotype 3; **GS3:** Serotype 3; **GS4:** PPSV23 serotypes without PCV13 serotypes; **GS5:** non-vaccine serotypes.

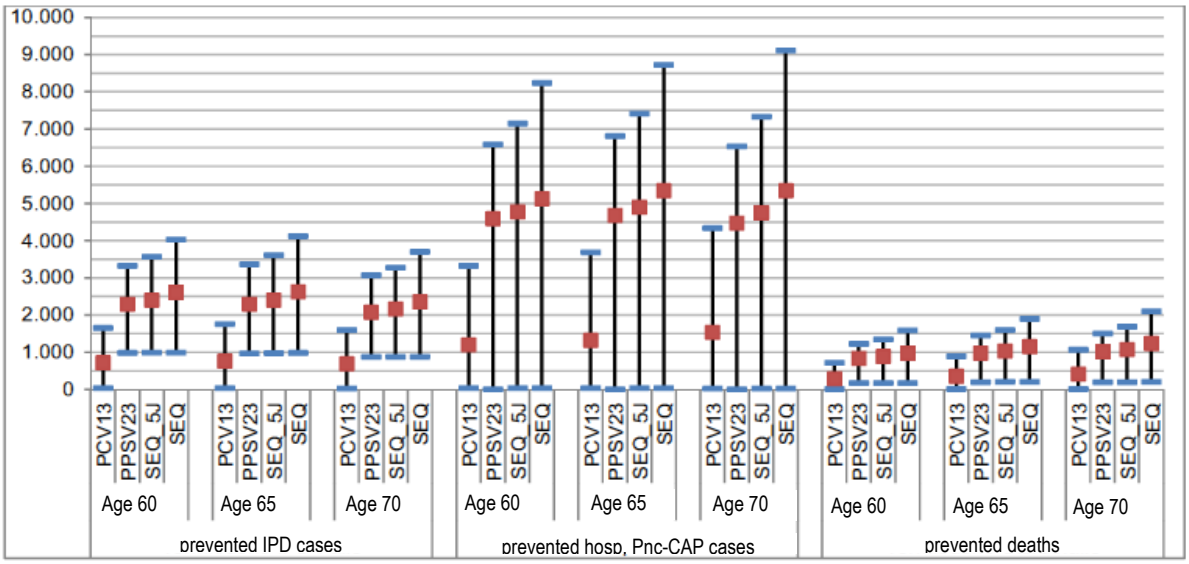
3.2 Results of single pneumococcal vaccination

3.2.1 Scenario A1: PPSV23 effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 and PCV13

3.2.1.1 Epidemiological results

Immunization of 60 year olds in the 2016-2030 period with PCV13 vaccination could prevent 712 (34-1649) IPD episodes, 1194 (33-3316) Pnc-CAPin episodes and 279 (6-713) disease-related deaths over the lifetime of vaccine recipients, compared with no vaccination. 2286 (982-3322) IPD, 4583 (0-6583) Pnc-CAPin episodes and 831 (163-1.222) disease-related deaths could be preventable with PPSV23 vaccination. The most effective strategy is sequential vaccination, which could prevent 2595 (989-4.027) IPD, 5125 (33-8234) Pnc-CAPin episodes and 970 (168-1581) disease-related deaths. PPSV23 is the most efficient vaccination in terms of the NNV to prevent one hospitalization or one disease-related death (see Figures 17, 18). With sequential vaccination, 6721 (2428-144,365) individuals would need to be vaccinated additionally with PCV13 in order to prevent one hospitalization, and 41,283 (15,954-1,116,813) additional people to prevent one disease-related death. Changing the vaccination age to 65 or 70 would improve the efficiency of the vaccinations.

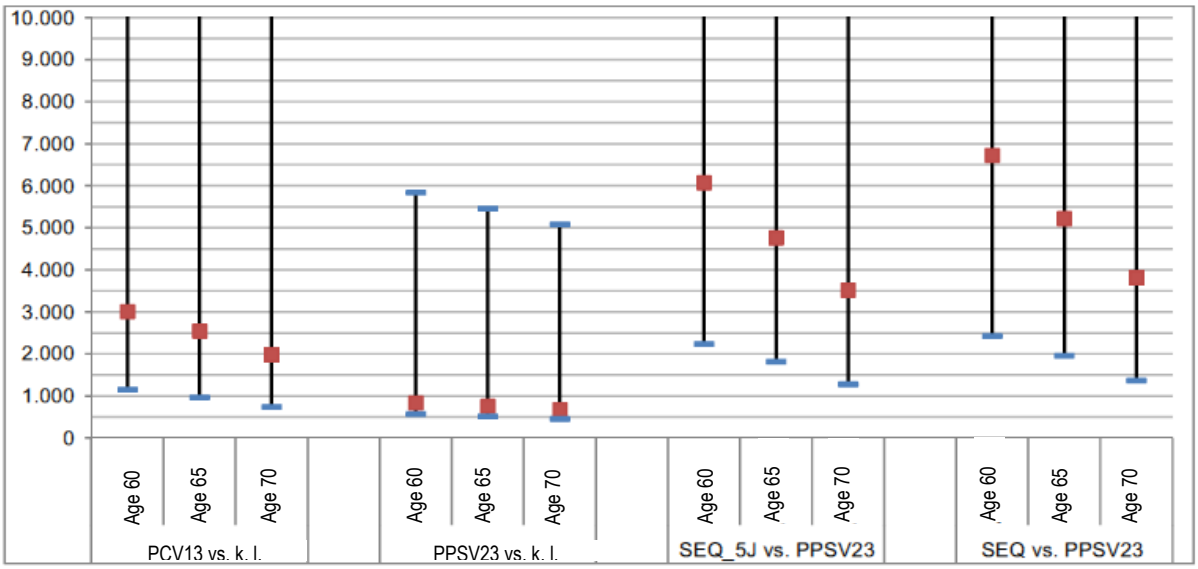
Figure 16: Single vaccination - Scenario A1: prevented cases



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period /Single vaccination with PPSV23 in the 2021-2030 period; **Age:** Age at initial vaccination

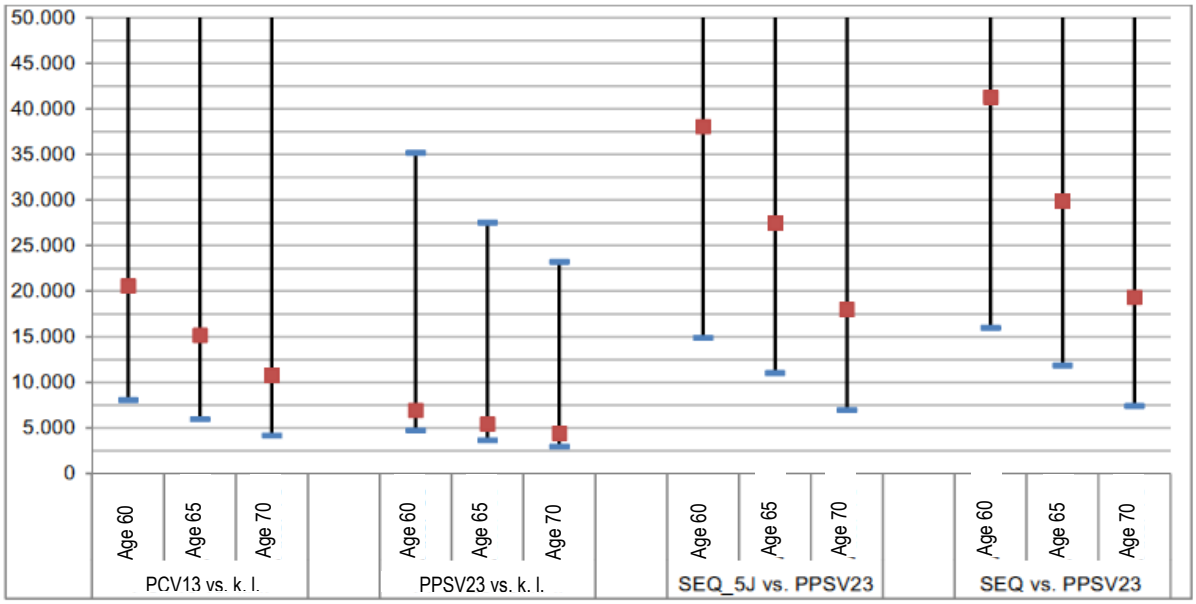
Figure 17: Single vaccination – Scenario A1: NNV to prevent one hospitalization



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. I.:** no vaccination; **Age:** Age at initial vaccination

Figure 18: Single vaccination – Scenario A1: NNV to prevent one death



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. l.:** no vaccination; **Age:** Age at initial vaccination

3.2.1.2 Health economics results

The PCV13 vaccination strategy is dominated by PPSV23 in the base case. The incremental cost effectiveness ratio of PPSV23 versus no vaccination is EUR 15,079-16,398 per QALY gained, depending on the age at vaccination. A sequential vaccination strategy would require additional spending of about EUR306,411-406,482 versus PPSV23 per QALY gained.

Table 8: Single vaccination - Scenario A1: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	PPSV23 vs. no vaccination	PCV13 vs. PPSV23	SEQ vs. PPSV23	SEQ_5J vs. PPSV23
60	EUR 15,079	dominated	EUR 406,482	EUR 366,499
65	EUR 16,398	dominated	EUR 355,525	EUR 318,812
70	EUR 16,130	dominated	EUR 338,779	EUR 306,411

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period

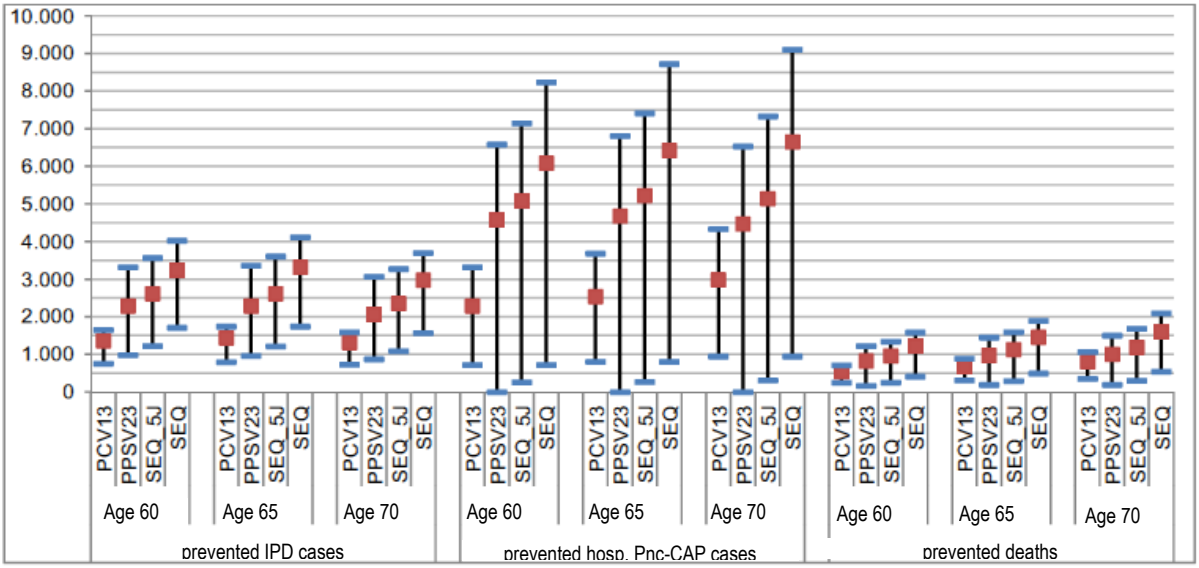
3.2.2 Scenario A2: PPSV23 effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 only

3.2.2.1 Epidemiological results

Immunization of 60 year olds in the 2016-2030 period with PCV13 vaccination could prevent 1362 (752-1649) IPD episodes, 2285 (721-3316) Pnc-CAPin episodes and 544 (246-713) disease-related deaths over the lifetime of vaccine recipients, compared with no vaccination. With PPSV23 vaccination, 2286 (982-3322) IPD episodes, 4583 (0-6583) Pnc-CAPin episodes and 831 (163-1222) disease-related deaths would be preventable. The most effective strategy is sequential vaccination, which could prevent 3245 (1706-4027) IPD episodes, 6086 (721-8234) Pnc-CAPin episodes and 1222 (409-1581) disease-related deaths.

PPSV23 is the most efficient vaccination in terms of the NNV to prevent one hospitalization or one disease-related death (see Figure 20 and 21). With sequential vaccination, 2323 (2428-3955) individuals would need additional vaccination with PCV13 in order to prevent one hospitalization, and 14,626 (15,954-23,277) additional vaccinations would be required to prevent one disease-related death. Changing the vaccination age to 65 or 70 would improve the efficiency of the vaccinations.

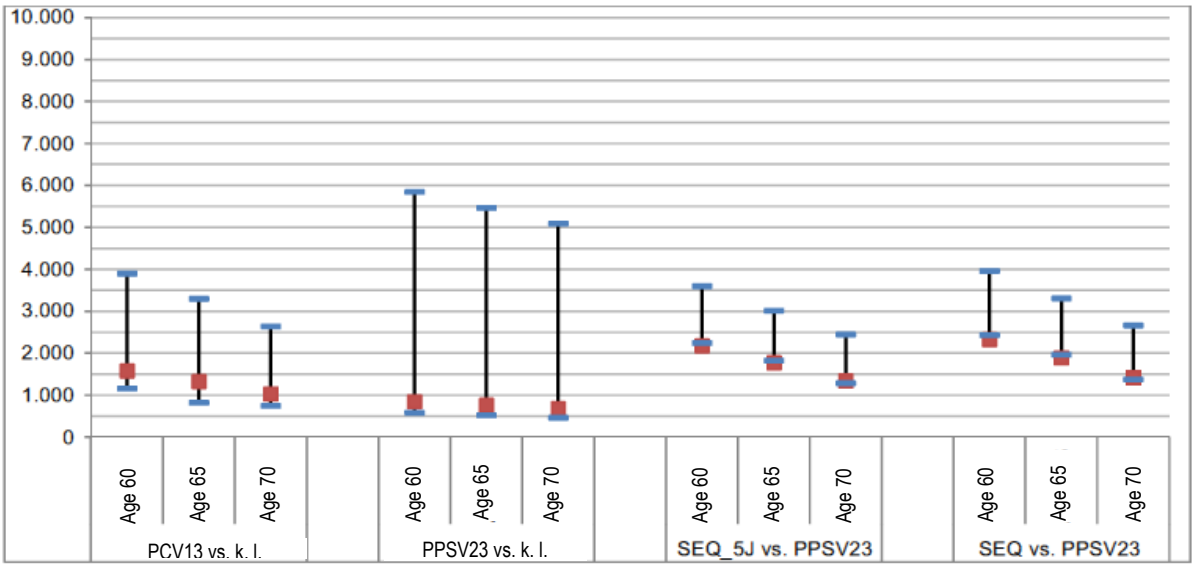
Figure 19: Single vaccination - Scenario A2: prevented cases



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **Age:** Age at initial vaccination

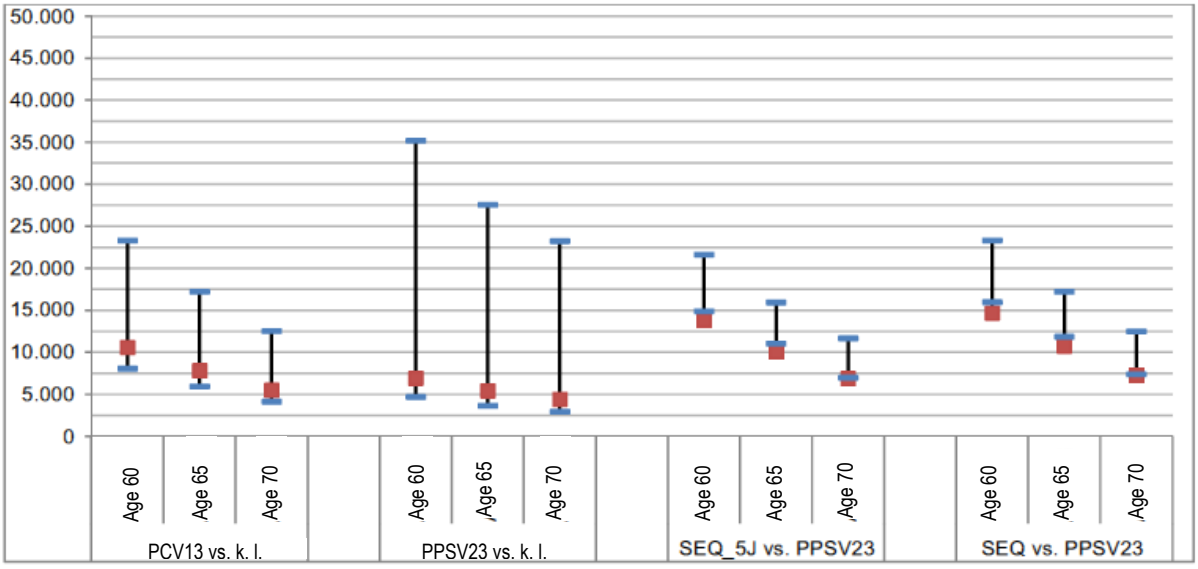
Figure 20: Single vaccination - Scenario A2: NNV to prevent one hospitalization



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. l.:** no vaccination; **Age:** Age at initial vaccination

Figure 21: Single vaccination - Scenario A2: NNV to prevent one death



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. l.:** no vaccination; **Age:** Age at initial vaccination

3.2.2.2 Health economics results

The PCV13 vaccination strategy is dominated by PPSV23 in the base case. The incremental cost effectiveness ratio of PPSV23 compared with no vaccination is EUR15,079-16,398 per QALY gained, depending on the age at vaccination. A sequential vaccination strategy would require additional spending of about EUR 85,310-107,252 versus PPSV23 per QALY gained.

Table 9: Single vaccination - Scenario A2: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	PPSV23 vs. no vaccination	PCV13 vs. PPSV23	SEQ vs. PPSV23	SEQ_5J vs. PPSV23
60	EUR 15,079	dominated	EUR 107,252	EUR 101,032
65	EUR 16,398	dominated	EUR 96,538	EUR 90,647
70	EUR 16,130	dominated	EUR 90,479	EUR 85,310

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period

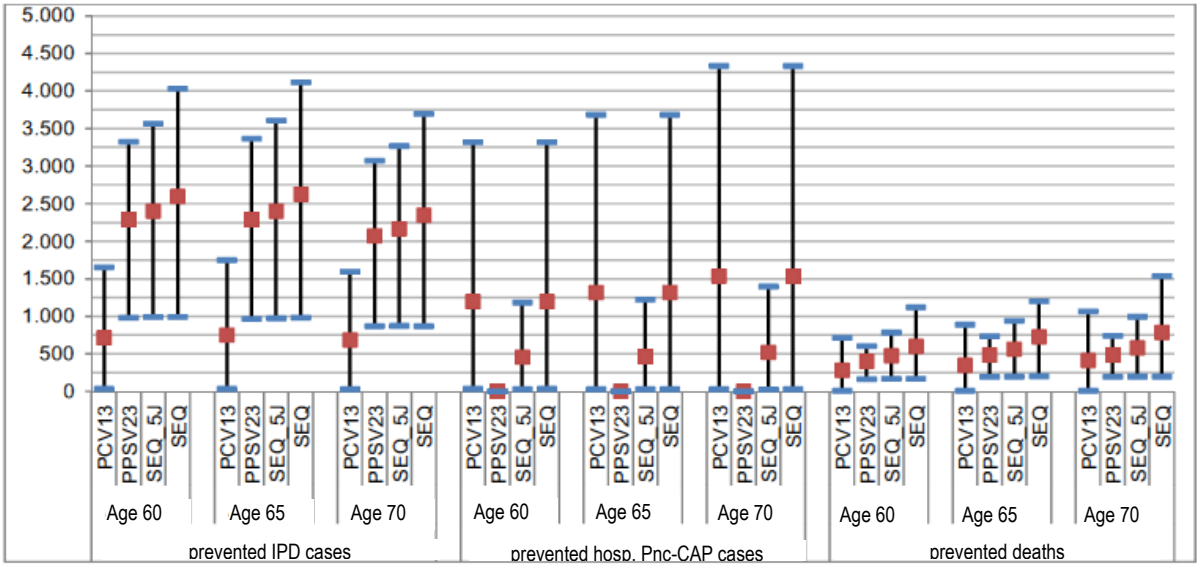
3.2.3 Scenario A3: PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 and PCV13

3.2.3.1 Epidemiological results

Immunization of 60 year olds in the 2016-2030 period with PCV13 vaccination could prevent 712 (34-1649) IPD episodes, 1194 (33-3316) Pnc-CAPin episodes and 279 (6-713) disease-related deaths over the lifetime of vaccination recipients, compared with no vaccination. With PPSV23 vaccination, 2286 (982-3322) IPD episodes, 0 Pnc-CAPin episodes and 400 (163-604) disease-related deaths would be preventable. The most effective strategy is sequential vaccination, which could prevent 2595 (989-4027) IPD episodes, 1194 (33-3316) Pnc-CAPin episodes and 600 (168-1118) disease-related deaths.

PPSV23 is the most efficient vaccination in terms of the NNV to prevent one hospitalization or one disease-related death (see Figure 23 and 24). With sequential vaccination, 3805 (1422- 144,365) individuals would need additional vaccination with PCV13 in order to prevent one hospitalization, and 28,704 (11,125-1,116,813) additional vaccinations would be required to prevent one disease-related death. Changing the vaccination age to 65 or 70 would improve the efficiency of the vaccinations.

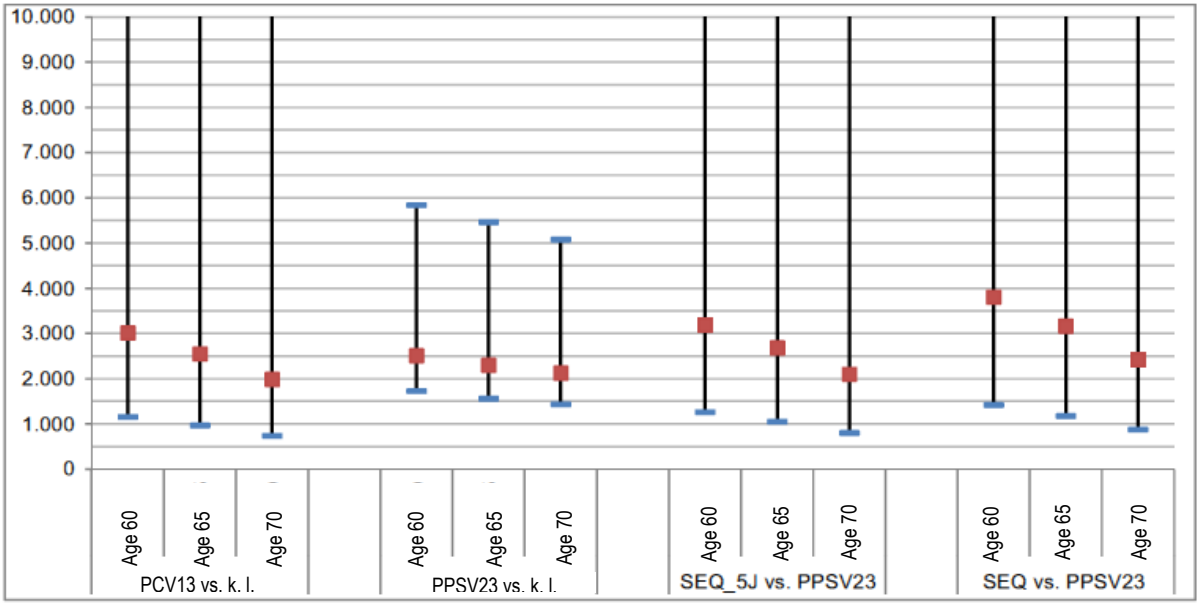
Figure 22: Single vaccination – Scenario A3: prevented cases



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **Age:** Age at initial vaccination

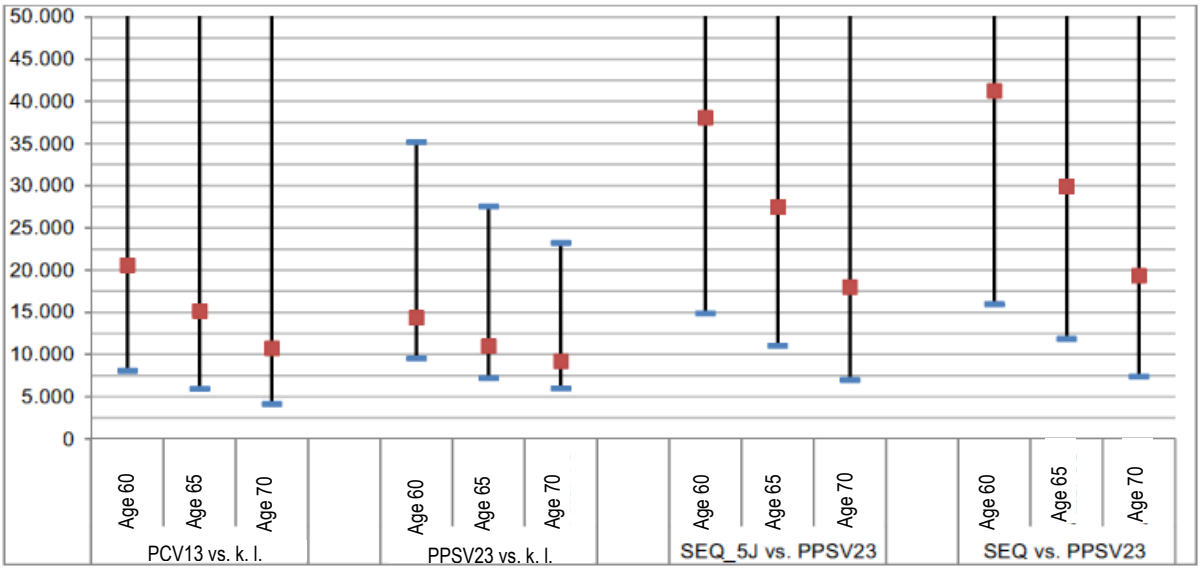
Figure 23: Single vaccination - Scenario A3: NNV to prevent one hospitalization



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. l.:** no vaccination; **Age:** Age at initial vaccination

Figure 24: Single vaccination - Scenario A3: NNV to prevent one death



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. I.:** no vaccination; **Age:** Age at initial vaccination

3.2.3.2 Health economics results

The PCV13 vaccination strategy is dominated by PPSV23 in the base case. The incremental cost effectiveness ratio of PPSV23 compared with no vaccination is EUR 37,673-38,860, depending on the age at vaccination. A sequential vaccination strategy would require additional spending of about EUR153,893-211,112 versus PPSV23 per QALY gained.

Table 10: Single vaccination - Scenario A3: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	PPSV23 vs. no vaccination	PCV13 vs. PPSV23	SEQ vs. PPSV23	SEQ_5J vs. PPSV23
60	EUR 38,613	dominated	EUR 211,112	EUR 178,595
65	EUR 37,673	dominated	EUR 192,552	EUR 163,370
70	EUR 38,860	dominated	EUR 178,843	EUR 153,893

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period

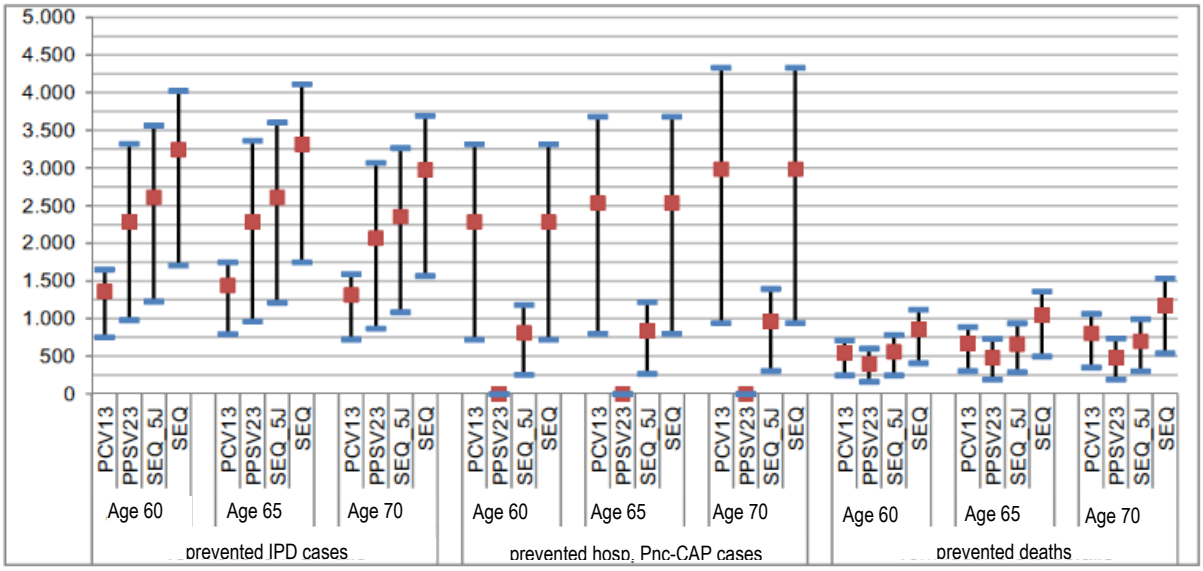
3.2.4 Scenario A4: PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 only with PPSV23

3.2.4.1 Epidemiological results

Immunization of 60 year olds in the 2016-2030 period with PCV13 vaccination could prevent 1362 (752-1649) IPD episodes, 2285 (721-3316) Pnc-CAPin episodes and 544 (246-713) disease-related deaths over the lifetime of vaccination recipients, compared with no vaccination. With PPSV23 vaccination, 2286 (982-3322) IPD episodes, 0 Pnc-CAPin episodes and 400 (163-604) disease-related deaths would be preventable. The most effective strategy is sequential vaccination, which could prevent 3245 (1706-4027) IPD episodes, 2285 (721-3316) Pnc-CAPin episodes and 864 (409-1118) disease-related deaths.

PCV13 is the most efficient vaccination in terms of the NNV to prevent one hospitalization or one disease-related death (see Figure 26 and 27). Changing the vaccination age to 65 or 70 would improve the efficiency of the vaccinations.

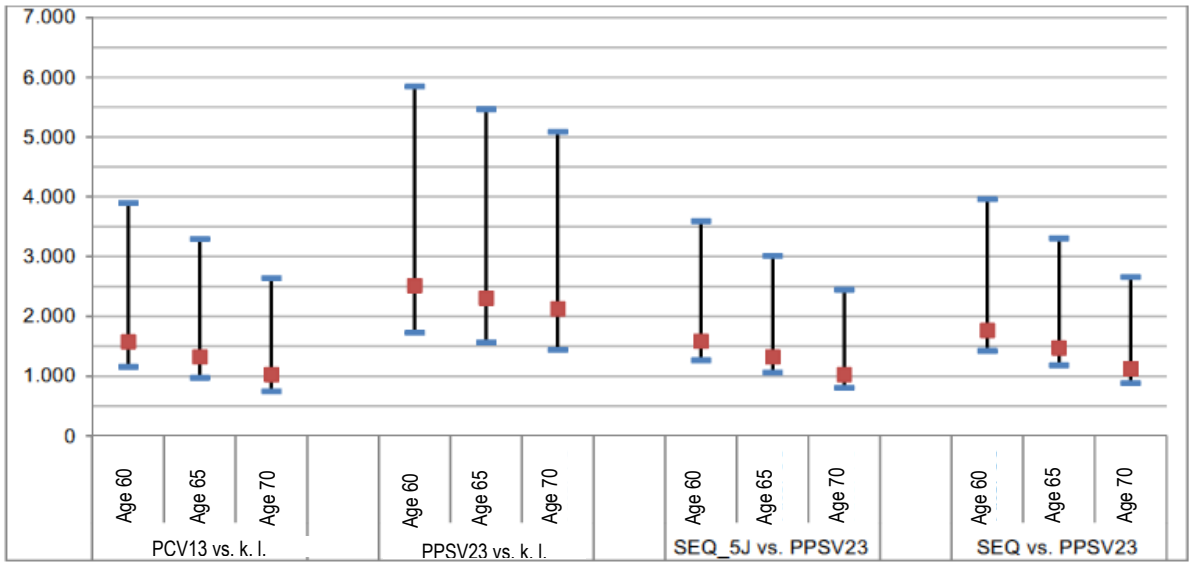
Figure 25: Single vaccination – Scenario A4: prevented cases



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **Age:** Age at initial vaccination

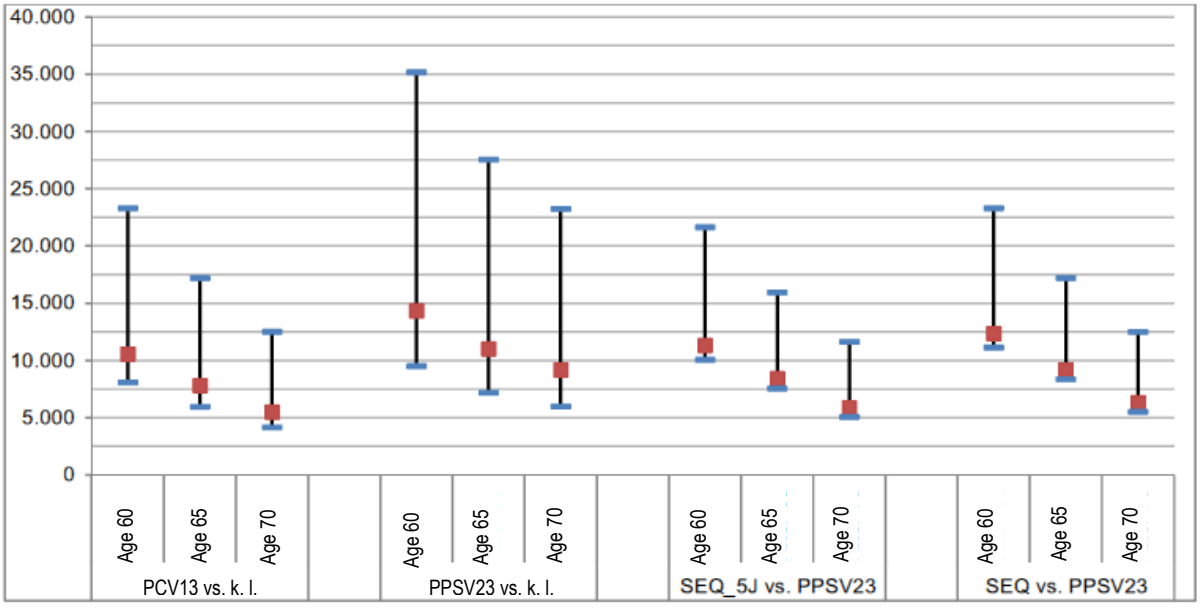
Figure 26: Single vaccination - Scenario A4: NNV to prevent one hospitalization



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. I.:** no vaccination; **Age:** Age at initial vaccination

Figure 27: Single vaccination - Scenario A4: NNV to prevent one death



■Results for the base case; ■Results for upper and lower limit of vaccination effectiveness (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period; **k. I.:** no vaccination; **Age:** Age at initial vaccination

3.2.4.2 Health economics results

The PCV13 vaccination strategy is dominated by PPSV23 in the base case. The incremental cost effectiveness ratio of PPSV23 compared with no vaccination is EUR 37,673-38,860, depending on the age at vaccination. A sequential vaccination strategy would require additional spending of about EUR63,604-81,775 versus PPSV23 per QALY gained.

Table 11: Single vaccination - Scenario A4: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	PPSV23 vs. no vaccination	PCV13 vs. PPSV23	SEQ vs. PPSV23	SEQ_5J vs. PPSV23
60	EUR 38,613	EUR 245,553	EUR 81,775	EUR 74,203
65	EUR 37,673	EUR 160,074	EUR 74,929	EUR 68,106
70	EUR 38,860	EUR 104,968	EUR 69,500	EUR 63,604

PCV13: Single vaccination with PCV13 in the 2016-2030 period; **PPSV23:** Single vaccination with PPSV23 in the 2016-2030 period; **SEQ:** Sequential vaccination with one PCV13 dose + PPSV23 booster six months later; **SEQ_5J:** Sequential vaccination in the 2016-2020 period/Single vaccination with PPSV23 in the 2021-2030 period

3.3 Results for revaccination

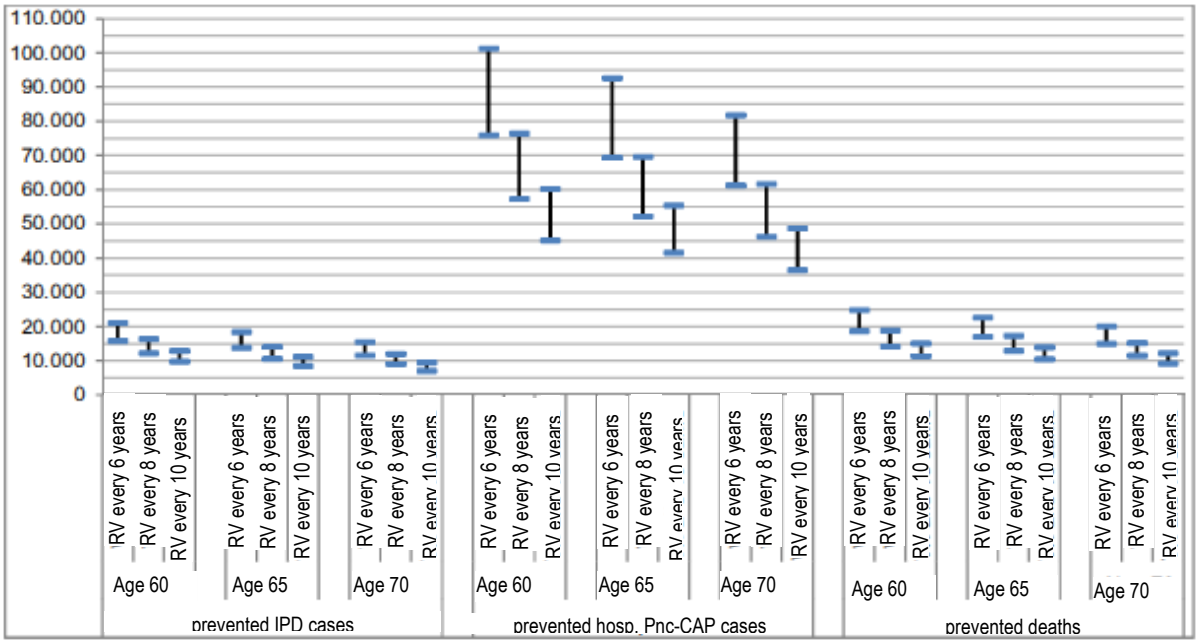
3.3.1 Scenario A1: PPSV23 effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 and PCV13

3.3.1.1 Epidemiological results

3.3.1.1.1 Initial vaccination with PPSV23 and revaccinations with PPSV23

Multiple lifelong revaccination with PPSV23 of individuals initially vaccinated in the 1996-2030 period could prevent an additional 7029-21,032 IPD episodes, 36,462-101,193 Pnc-CAPin episodes and 9117-24,745 disease-related deaths over the lifetime of vaccine recipients versus single vaccination with PPSV23, depending on revaccination frequency and age at initial vaccination. The most effective of the analyzed strategies is initial vaccination at age 60 with revaccination every six years (see Figure 28). This vaccination strategy is also the most inefficient option in terms of the NNV to prevent one hospitalization or one disease-related death, but the differences are marginal (see Figure 29 and 30).

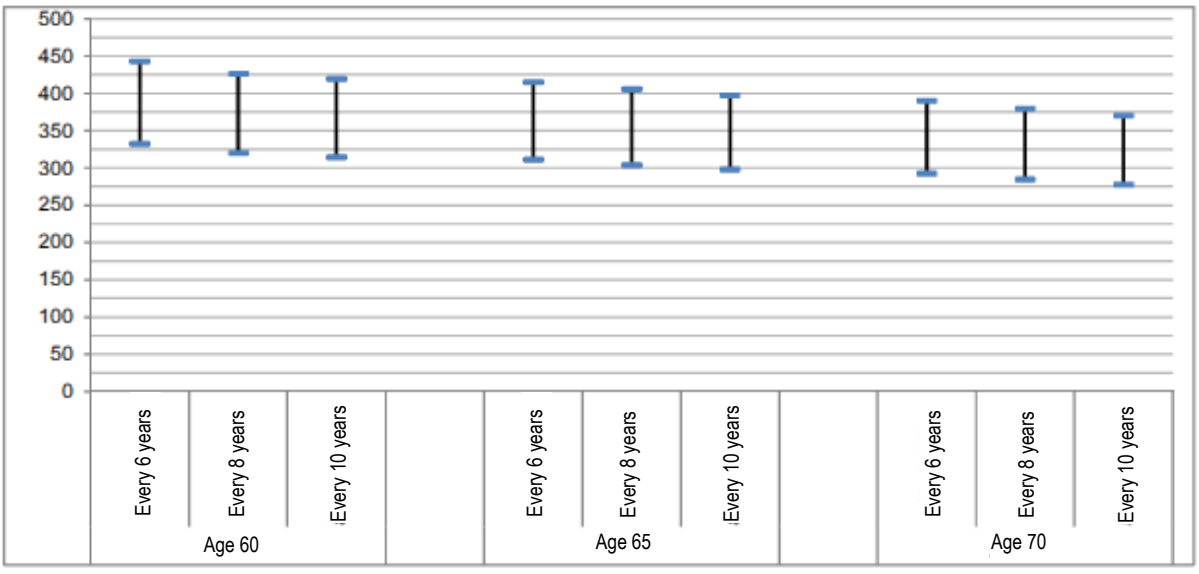
Figure 28: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A1: Additionally prevented cases



Results for reduction of effectiveness of revaccination by 25% and 0% versus initial PPSV23 vaccination (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

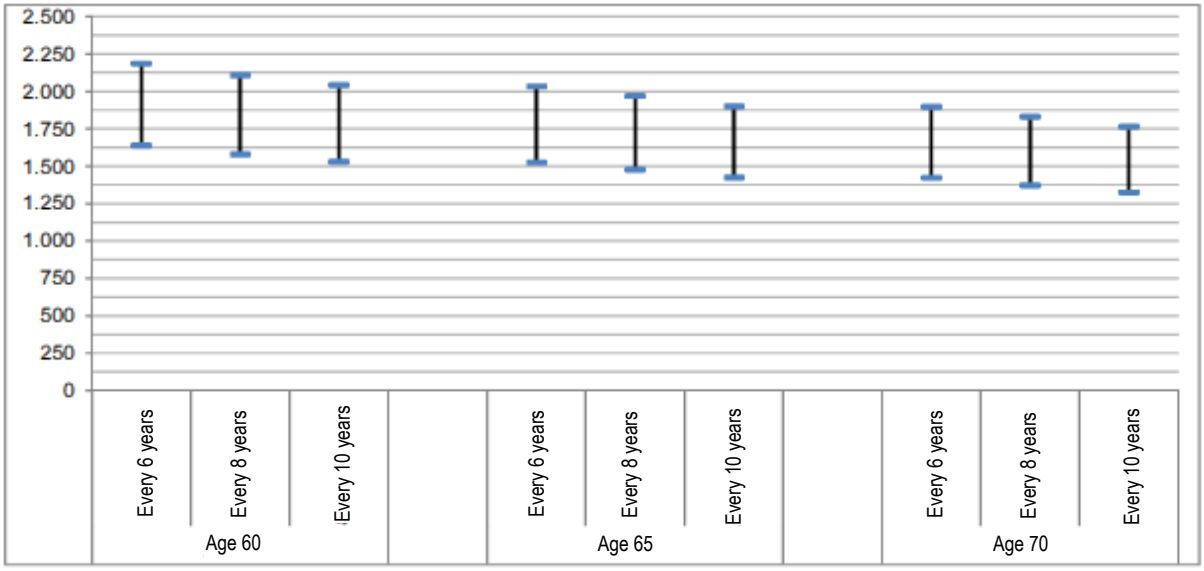
Figure 29: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A1: NNV to prevent one additional hospitalization



Results for reduction of effectiveness of revaccination by 25% and 0% versus initial PPSV23 vaccination (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 30: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A1: NNV to prevent one additional death



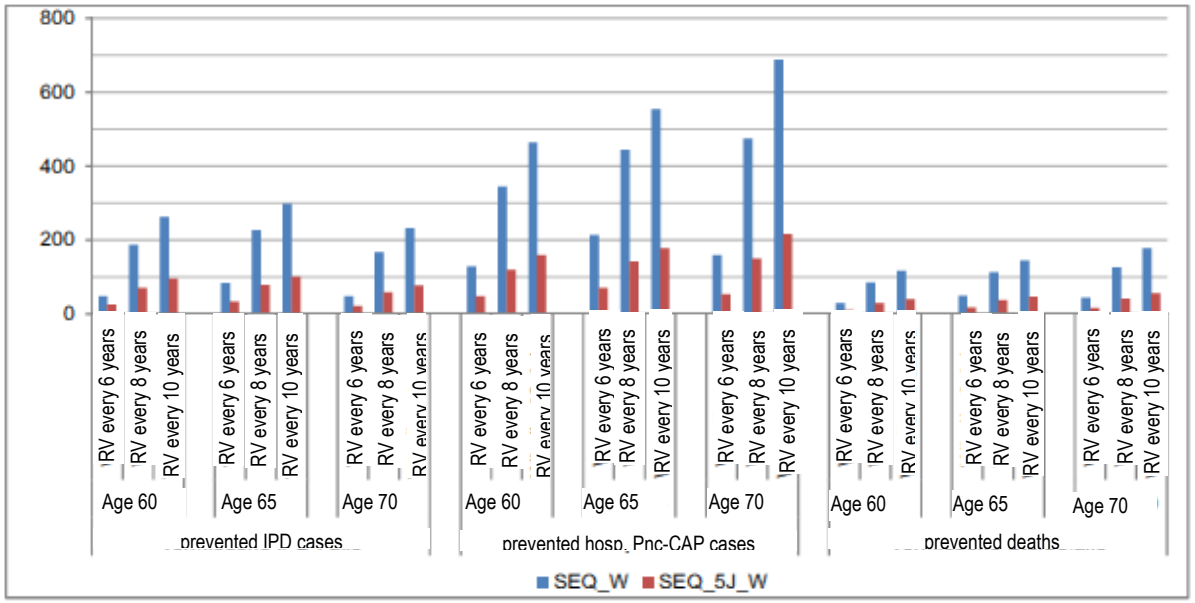
Results for reduction of effectiveness of revaccination by 25% and 0% versus initial PPSV23 vaccination (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

3.3.1.1.2 Sequential initial vaccination and revaccinations with PPSV23

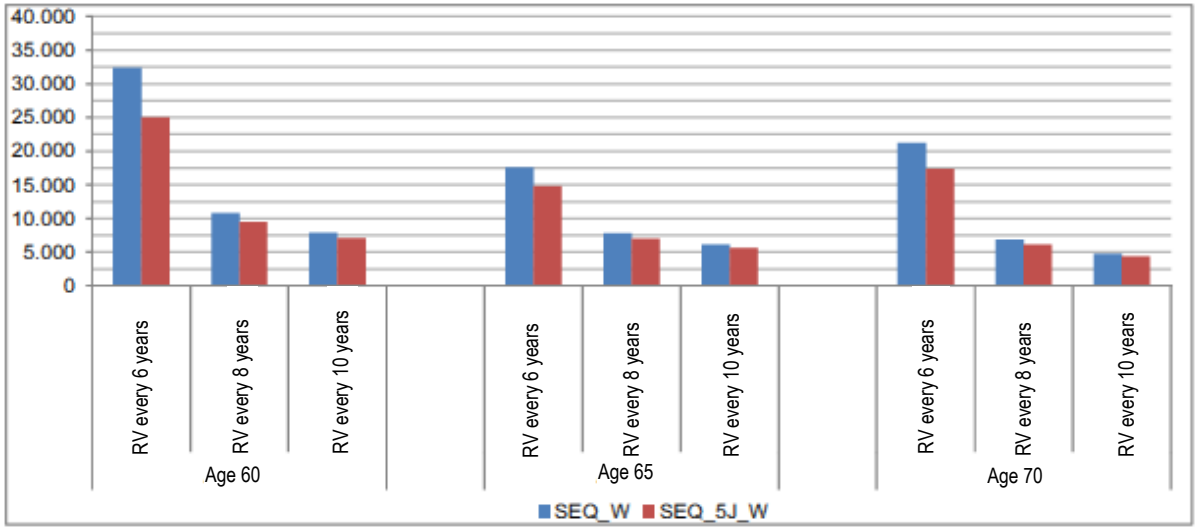
Initial administration of sequential vaccination instead of PPSV23 in the 2016-2030 period could prevent an additional 48-297 IPD episodes, 128-688 Pnc-CAPin episodes and 29-177 disease-related deaths over the lifetime of the vaccination recipients depending on the frequency of vaccination and age at initial vaccination. The most effective of the analyzed strategies is sequential initial vaccination at age 60 with revaccination every six years (see Figure 31). However, this vaccination strategy provides the smallest effectiveness gain versus revaccination with initial PPSV23 vaccination (see Figure 32 and 33) as the higher effectiveness of sequential vaccination is due in particular to the longer duration of immunity with PCV13. This benefit of sequential vaccination is lost in large part with revaccination after six years unless the effectiveness of the revaccination falls below a certain threshold. This is not the case in the presence of 25% lower efficacy of revaccinations with PPSV23, so a graph has not been provided (but see Tables 12-14 on incremental cost effectiveness).

Figure 31: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A1: additionally prevented cases



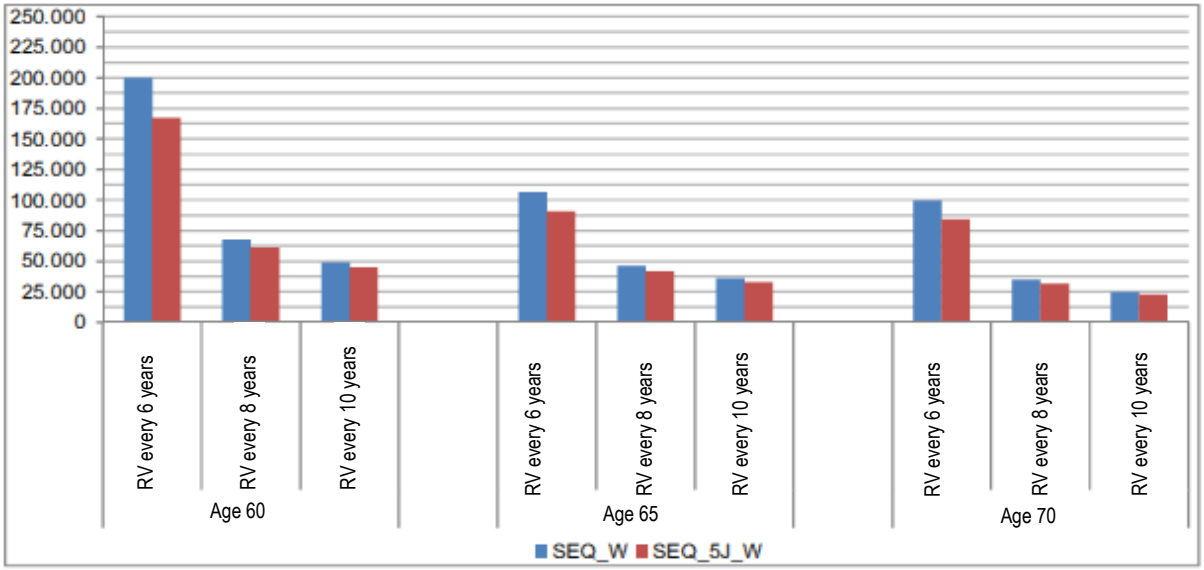
PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 32: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A1: NNV to prevent one additional hospitalization



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 33: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A1: NNV to prevent one additional death



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

3.3.1.2 Health economics results

3.3.1.2.1 Initial vaccination with PPSV23 and revaccinations with PPSV23

If PPSV23 revaccination is as effective as initial PPSV23 vaccination, then the incremental cost effectiveness ratio is EUR 8990 – 11,150 per QALY gained, depending on age at initial vaccination and frequency of revaccination. If revaccination is 25% less effective than the initial vaccination, then the ICER rises to EUR 13,731-16,585 per QALY gained. With the frequencies analyzed, the interval of time between vaccinations has little impact on the incremental cost effectiveness ratio.

Table 12: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A1: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 11,150	EUR 10,502	EUR 10,234
65	EUR 10,515	EUR 10,066	EUR 9,793
70	EUR 9,819	EUR 9,399	EUR 8,990
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 16,585	EUR 15,697	EUR 15,346
65	EUR 15,775	EUR 15,154	EUR 14,778
70	EUR 14,864	EUR 14,293	EUR 13,731

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

3.3.1.2.2 Sequential initial vaccination and PPSV23 revaccinations

If PPSV23 revaccination is as effective as initial PPSV23 vaccination, then the incremental cost effectiveness ratio is EUR 413,750-5,009,010 per QALY gained, depending on age at initial vaccination and frequency of revaccination. The incremental cost effectiveness ratio rises with a reduction in the interval between initial vaccination and revaccination. If revaccination is 25% less effective than the initial vaccination, then the additional cost per QALY gained declines marginally with sequential initial vaccination strategies.

Table 13: Vaccination strategy SEQ_W vs. PPSV23_W - Scenario A1: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 4,823,633	EUR 686,869	EUR 476,626
65	EUR 1,715,852	EUR 537,524	EUR 413,750
70	EUR 5,009,010	EUR 597,985	EUR 414,911
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 4,689,881	EUR 686,679	EUR 476,624
65	EUR 1,693,985	EUR 537,315	EUR 413,748
70	EUR 4,731,080	EUR 597,646	EUR 414,910

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

Table 14: Vaccination strategy SEQ_5J_W vs. PPSV23_W - Scenario A1: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 2,810,187	EUR 598,592	EUR 425,785
65	EUR 1,270,467	EUR 468,585	EUR 367,358
70	EUR 2,645,213	EUR 519,401	EUR 370,209
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 2,758,938	EUR 598,443	EUR 425,783
65	EUR 1,257,226	EUR 468,422	EUR 367,357
70	EUR 2,560,204	EUR 519,143	EUR 370,208

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

3.3.2 Scenario A2: PPSV23 effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 only with PPSV23

3.3.2.1 Epidemiological results

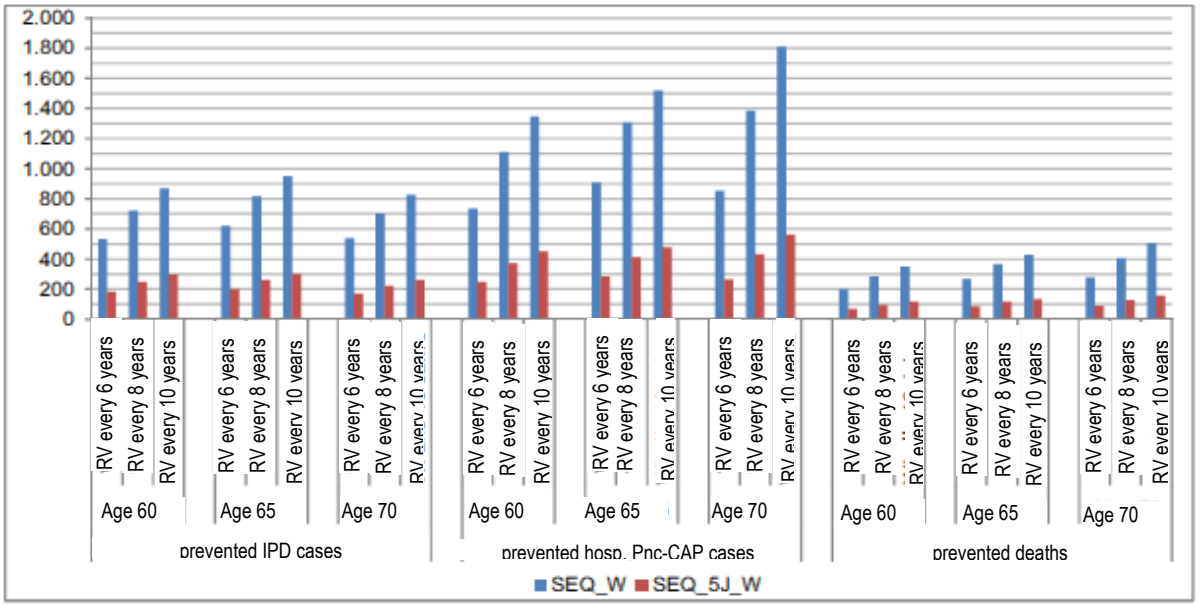
3.3.2.1.1 Initial vaccination with PPSV23 and PPSV23 revaccinations

The results are as given for Scenario A1 as the PPSV23 parameters are the same as for Scenario A1.

3.3.2.1.2 Sequential initial vaccination and revaccinations with PPSV23

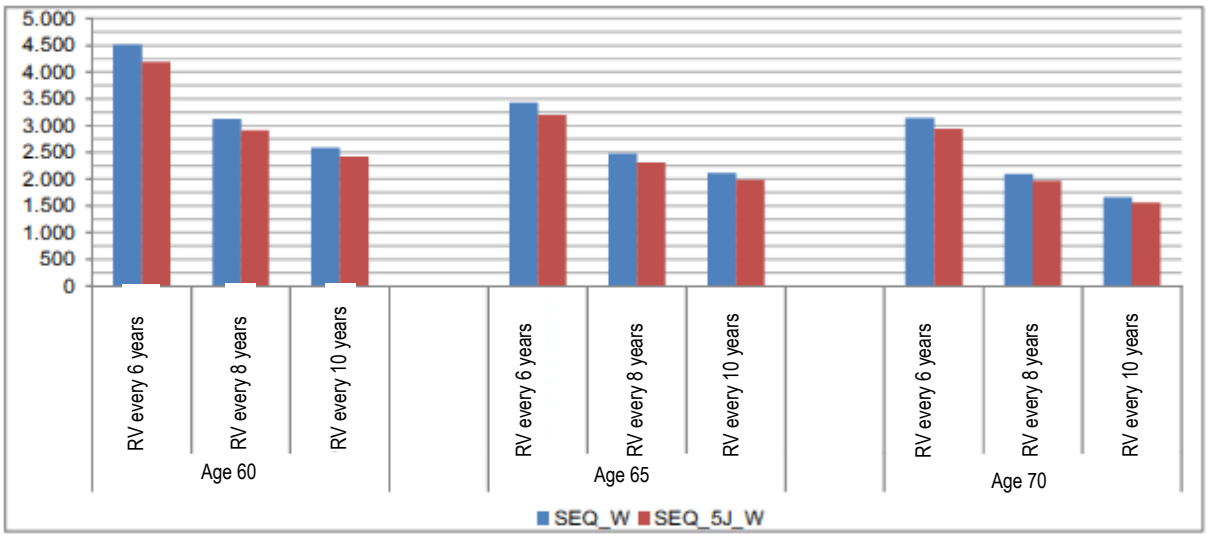
Initial administration of sequential vaccination instead of PPSV23 in the 2016-2030 period could prevent an additional 531-950 IPD episodes, 734-1809 Pnc-CAPin episodes and 198-504 disease-related deaths over the lifetime of the vaccine recipients depending on the frequency of vaccination and age at initial vaccination. The most effective of the analyzed strategies is sequential initial vaccination at age 60 with revaccination every six years (see Figure 34). However, this vaccination strategy is associated with the smallest effectiveness gain versus revaccination with initial PPSV23 vaccination (see Figure 35 and 36) as the higher effectiveness of sequential vaccination is due in particular to the longer duration of immunity with PCV13. This benefit of sequential vaccination is lost in large part with revaccination after six years unless the effectiveness of the revaccination falls below a certain threshold. This is not the case in the presence of 25% lower efficacy of revaccinations with PPSV23, so a graph has not been provided (but see Tables 12, 15 and 16 on incremental cost effectiveness).

Figure 34: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A2: Additionally prevented cases



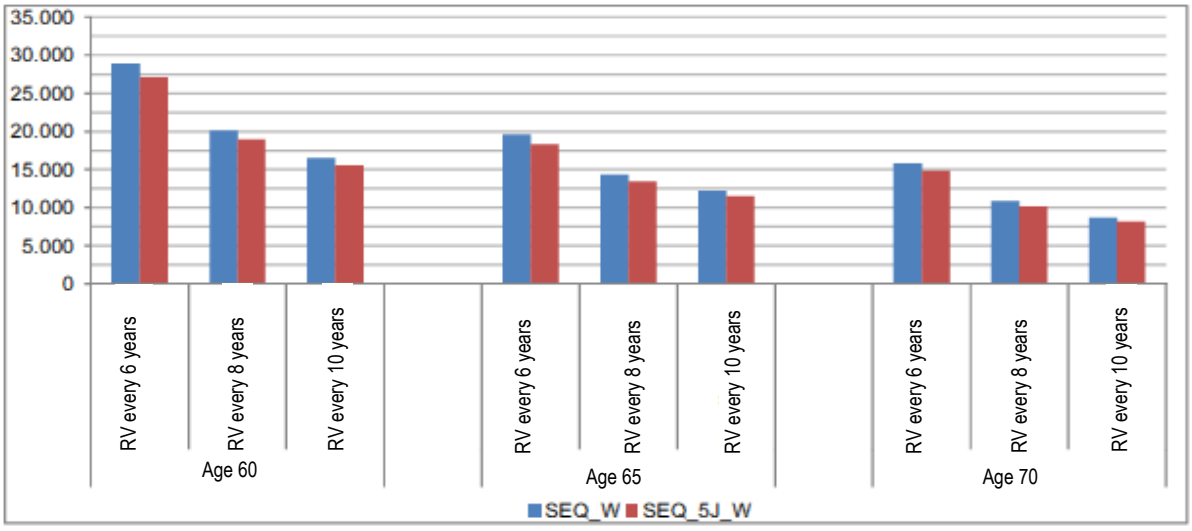
PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 35: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A2: NNV to prevent one additional hospitalization



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 36: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A2: NNV to prevent one additional death



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

3.3.2.2 Health economics results

3.3.2.2.1 Initial vaccination with PPSV23 and revaccinations with PPSV23

The results are as given for Scenario A1 as the PPSV23 parameters are the same as for Scenario A1.

3.3.2.2.2 Sequential initial vaccination and revaccinations with PPSV23

If PPSV23 revaccination is as effective as initial PPSV23 vaccination, then the incremental cost effectiveness ratio is EUR 101,012-191,548 per QALY gained, depending on age at initial vaccination and frequency of revaccination. The incremental cost effectiveness ratio rises with reduction of the interval between initial vaccination and revaccination. If revaccination is 25% less effective than the initial vaccination, then the additional cost per gained QALY of the strategies with sequential initial vaccination declines marginally or remains constant.

Table 15: Vaccination strategy SEQ_W vs. PPSV23_W - Scenario A2: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 191,548	EUR 137,998	EUR 116,810
65	EUR 158,678	EUR 119,263	EUR 104,983
70	EUR 168,408	EUR 119,461	EUR 101,012
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 169,886	EUR 136,387	EUR 116,810
65	EUR 143,648	EUR 118,168	EUR 104,982
70	EUR 149,015	EUR 118,392	EUR 101,012

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

Table 16: Vaccination strategy SEQ_5J_W vs. PPSV23_W - Scenario A2: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 179,637	EUR 129,773	EUR 109,942
65	EUR 148,210	EUR 111,732	EUR 98,449
70	EUR 157,547	EUR 112,209	EUR 95,035
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 159,486	EUR 128,267	EUR 109,942
65	EUR 134,322	EUR 110,716	EUR 98,449
70	EUR 139,653	EUR 111,217	EUR 95,035

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

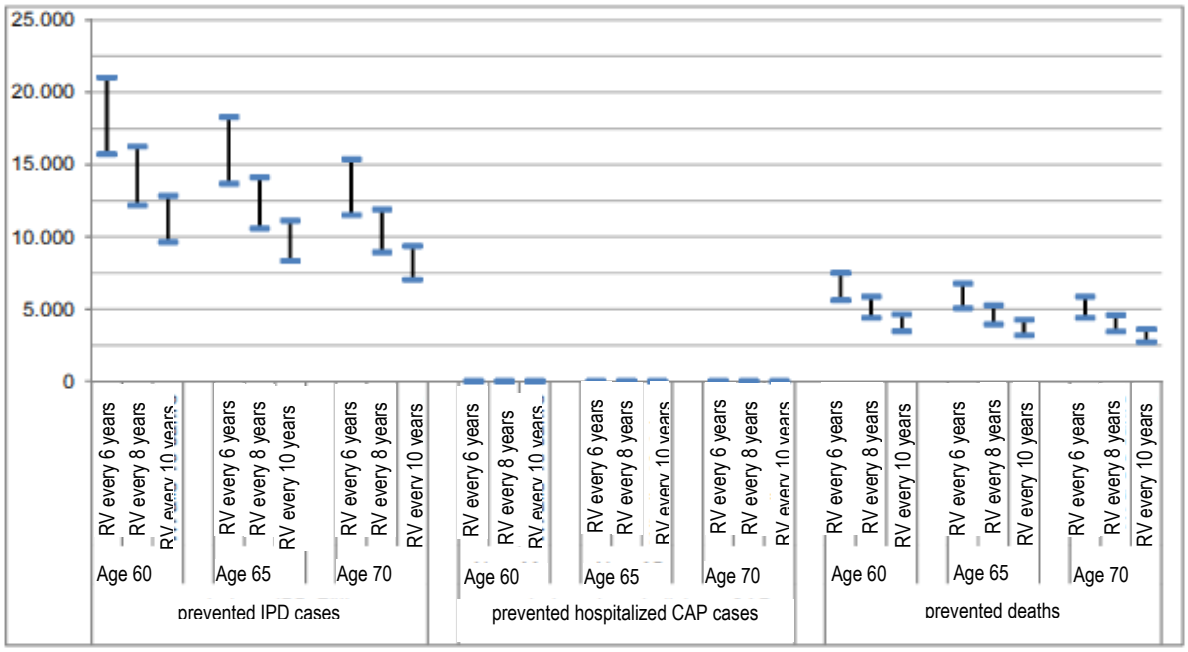
3.3.3 Scenario A3: PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 and PCV13

3.3.3.1 Epidemiological results

3.3.3.1.1 Initial vaccination with PPSV23 and PPSV23 revaccinations

Multiple lifelong revaccination with PPSV23 of individuals first vaccinated in the 1996-2030 period could prevent 7029-21,032 IPD episodes, 0 Pnc-CAPin episodes and 2714-7524 disease-related deaths in the 60+ age group versus single vaccination with PPSV23, depending on the frequency of vaccination and age at initial vaccination. The most effective of the analyzed strategies is initial vaccination at the age of 60 years with revaccination every six years (see Figure 37). This vaccination strategy is also the most inefficient option in terms of the number needed to vaccinate to prevent one hospitalization or one disease-related death, but the differences are marginal (see Figure 38 and 39).

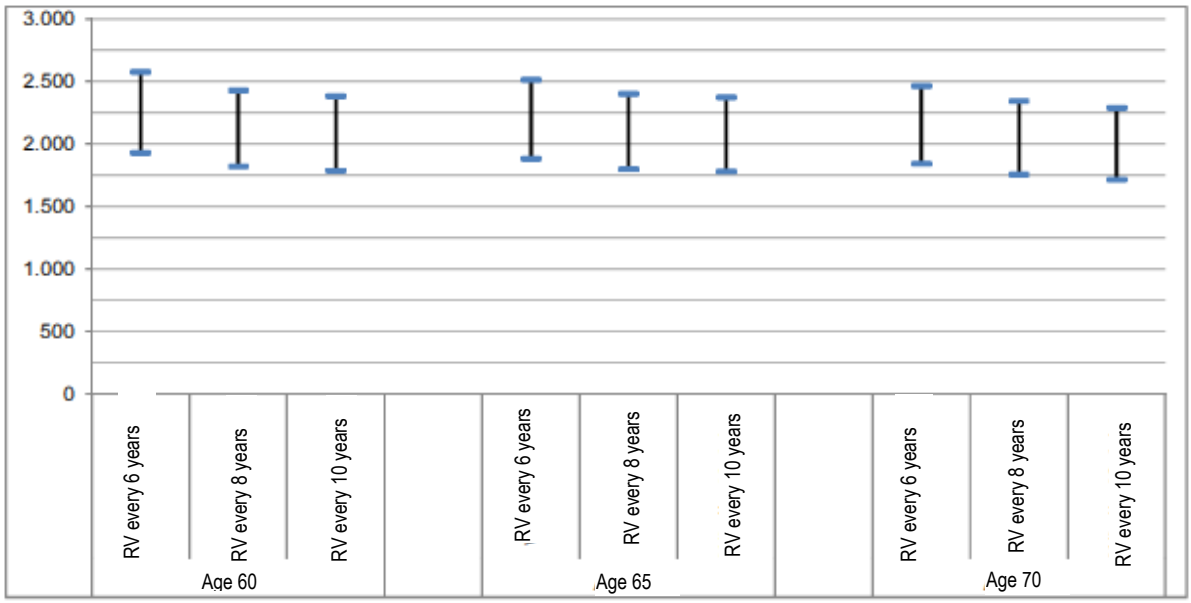
Figure 37: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A3: additionally prevented cases



Results for reduction of effectiveness of revaccination by 25% and 0% versus initial PPSV23 vaccination (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

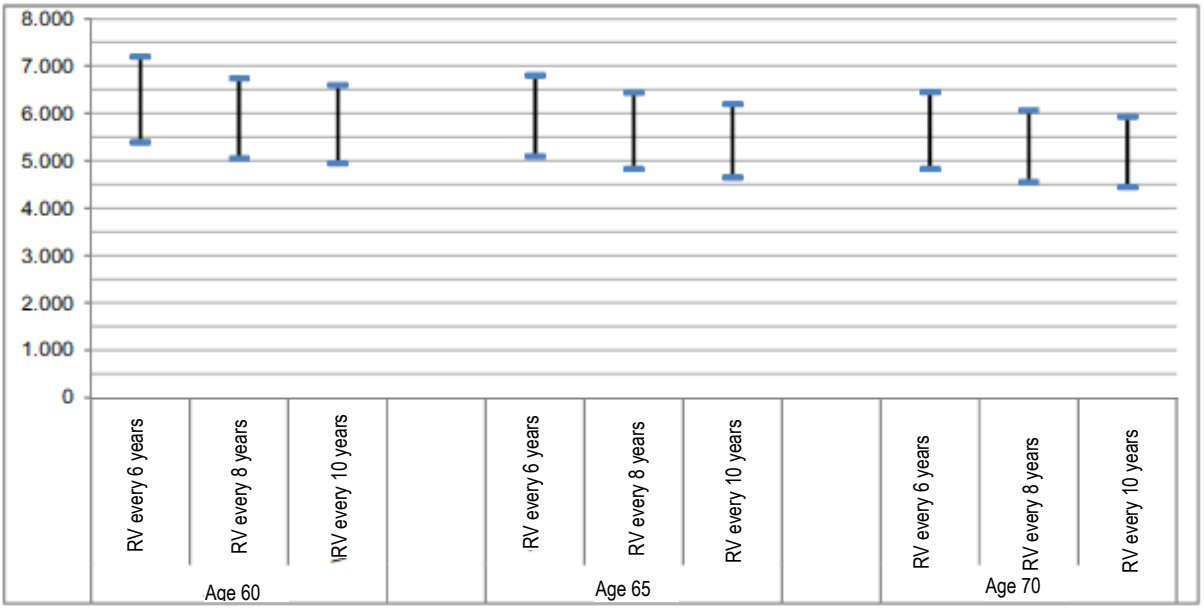
Figure 38: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A3: NNV to prevent one additional hospitalization



Results for reduction of effectiveness of revaccination by 25% and 0% versus initial PPSV23 vaccination (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 39: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A3: NNV to prevent one additional death



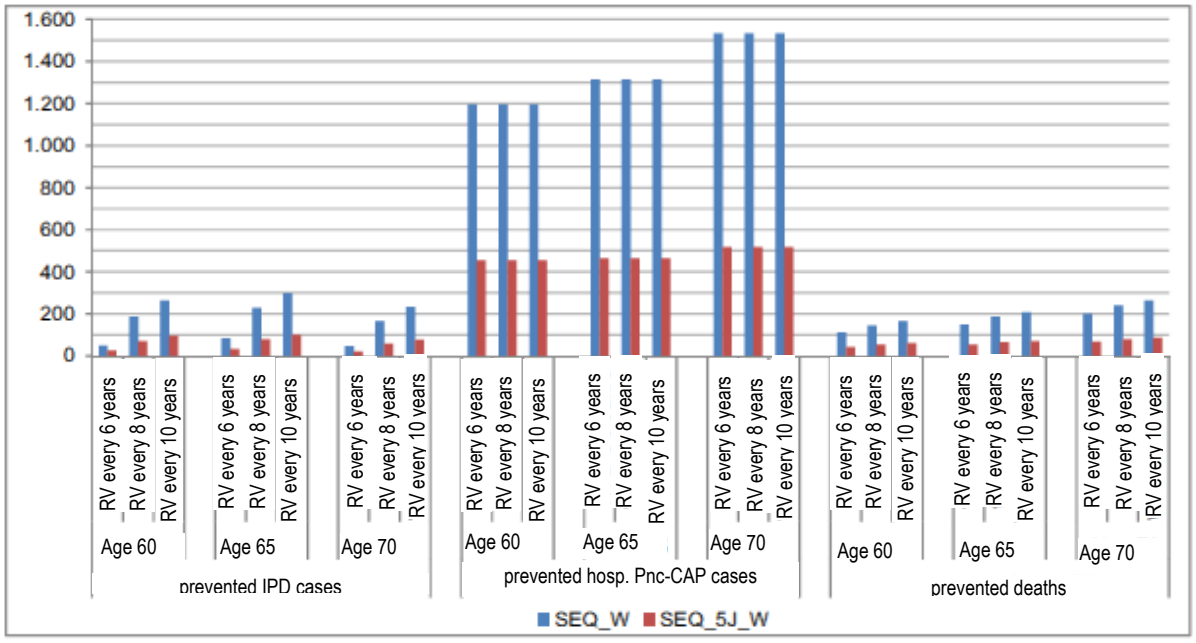
Results for reduction of effectiveness of revaccination by 25% and 0% versus initial PPSV23 vaccination (see section 3.6, Table 6)

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

3.3.3.1.2 Sequential initial vaccination and revaccinations with PPSV23

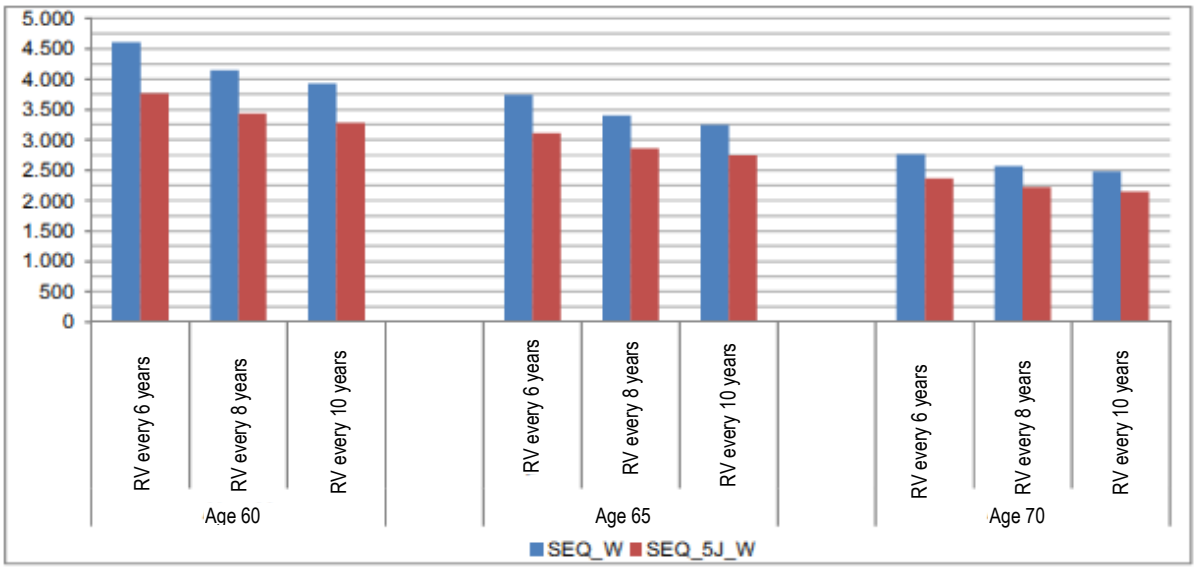
Initial administration of sequential vaccination instead of PPSV23 in the 2016-2030 period could prevent an additional 48-297 IPD episodes, 1194-1534 Pnc-CAPin episodes and 134-282 disease-related deaths over the lifetime of the vaccination recipients, depending on the frequency of vaccination and age at initial vaccination. The most effective of the analyzed strategies is sequential initial vaccination at age 60 with revaccination every six years (see Figure 40). However, this vaccination strategy provides the smallest effectiveness gain versus revaccination with initial PPSV23 vaccination, as the higher effectiveness of sequential vaccination is due in particular to the longer duration of immunity with PCV13. This benefit of sequential vaccination is lost in large part with revaccination after six years unless the effectiveness of the revaccination falls below a certain threshold (see Figure 41 and 42). This is not the case in the presence of 25% lower effectiveness of revaccinations with PPSV23, so a graph has not been provided (but see Tables 17-19 on incremental cost effectiveness).

Figure 40: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A3: Additionally prevented cases



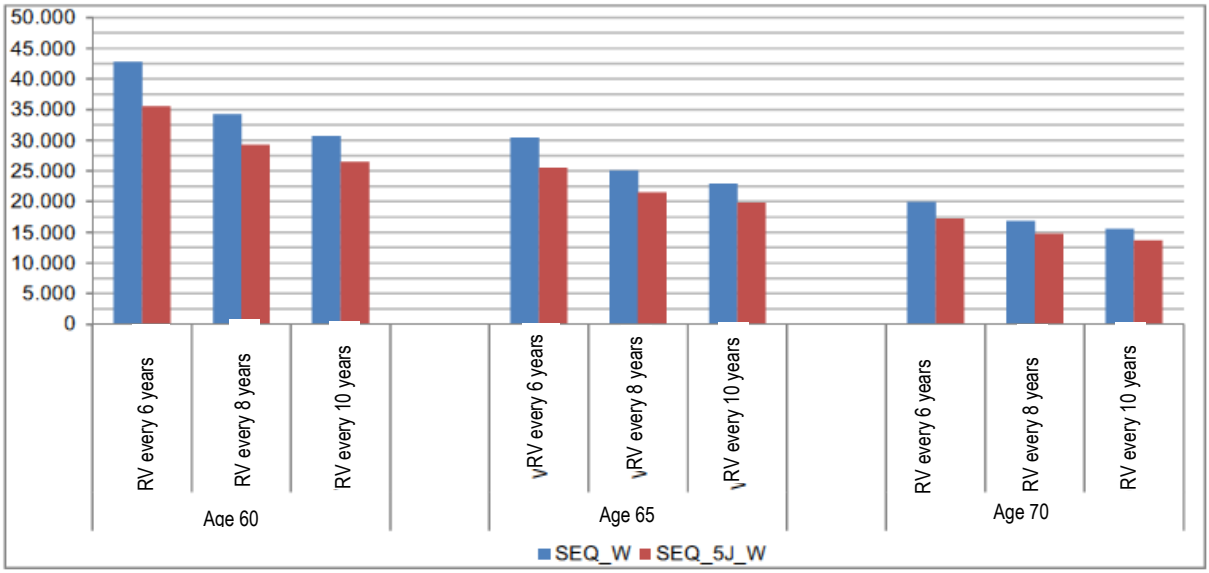
PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 41: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A3: NNV to prevent one additional hospitalization



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 42: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A3: NNV to prevent one additional death



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

3.3.3.2 Health economics results

3.3.3.2.1 Initial vaccination with PPSV23 and revaccinations with PPSV23

If PPSV23 revaccination is as effective as initial PPSV23 vaccination, then the incremental cost effectiveness ratio is EUR 37,646-40,777 per QALY gained, depending on age at initial vaccination and frequency of revaccination. If revaccination is 25% less effective than the initial vaccination, then the ICER rises to EUR 52,035-56,338 per QALY gained. With the frequencies analyzed, the interval of time between vaccinations has little impact on the incremental cost effectiveness ratio.

Table 17: Vaccination strategy PPSV23_W vs. PPSV23 - Scenario A3: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 40,741	EUR 38,449	EUR 38,156
65	EUR 40,777	EUR 38,858	EUR 38,329
70	EUR 40,346	EUR 38,451	EUR 37,646
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 56,241	EUR 53,043	EUR 52,662
65	EUR 56,338	EUR 53,634	EUR 52,908
70	EUR 55,773	EUR 53,118	EUR 52,035

PPSV23: Single vaccination with PPSV23 in the 2016-2030 period; **PPSV23_W:** Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

3.3.3.2.2 Sequential initial vaccination and revaccinations with PPSV23

If PPSV23 revaccination is as effective as initial PPSV23 vaccination, then the incremental cost effectiveness ratio is EUR 186,257-297,556 per QALY gained, depending on age at initial vaccination and frequency of revaccination. The incremental cost effectiveness ratio rises with a reduction in the interval between initial vaccination and revaccination. If revaccination is 25% less effective than the initial vaccination, then the additional cost per QALY gained declines marginally with sequential initial vaccination strategies or remains constant.

Table 18: Vaccination strategy SEQ_W vs. PPSV23_W - Scenario A3: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 297,556	EUR 242,729	EUR 221,234
65	EUR 256,859	EUR 215,087	EUR 200,469
70	EUR 233,102	EUR 198,850	EUR 186,257
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 297,443	EUR 242,729	EUR 221,234
65	EUR 256,775	EUR 215,087	EUR 200,469
70	EUR 233,034	EUR 198,850	EUR 186,257

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

Table 19: Vaccination strategy SEQ_5J_W vs. PPSV23_W - Scenario A3: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 241,218	EUR 202,174	EUR 186,205
65	EUR 210,545	EUR 180,295	EUR 169,339
70	EUR 194,841	EUR 169,265	EUR 159,594
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 241,115	EUR 202,174	EUR 186,205
65	EUR 210,467	EUR 180,295	EUR 169,339
70	EUR 194,776	EUR 169,265	EUR 159,594

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

3.3.4 Scenario A4: PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 only with PPSV23

3.3.4.1 Epidemiological results

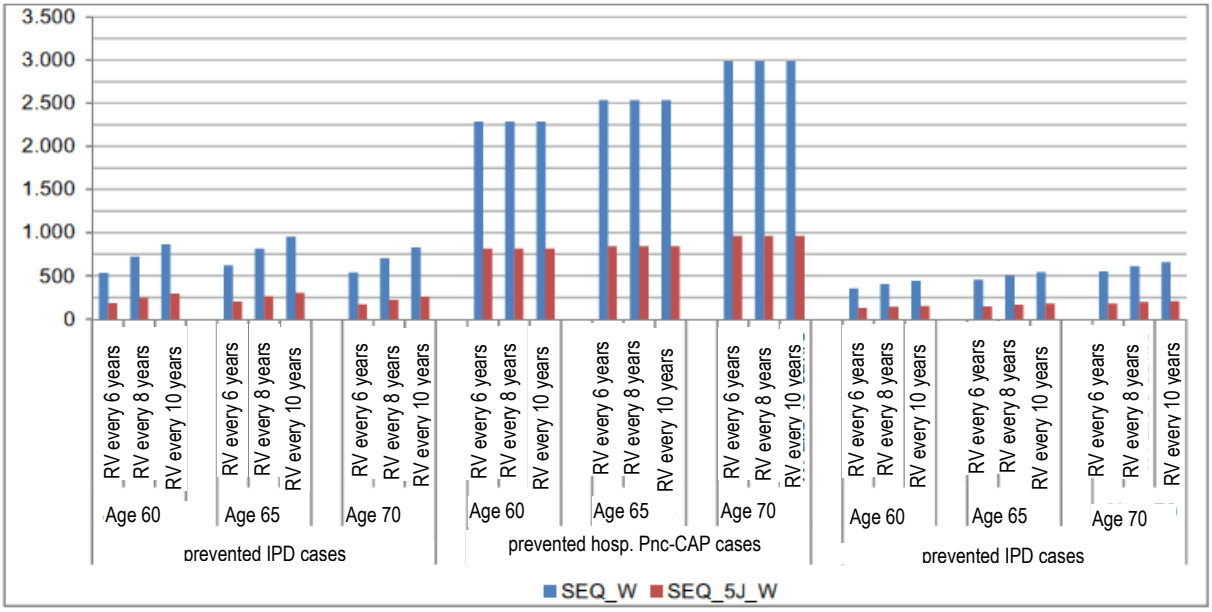
3.3.4.1.1 Initial vaccination with PPSV23 and revaccinations with PPSV23

The results are as given for Scenario A3 as the PPSV23 parameters are the same as for Scenario A3.

3.3.4.1.2 Sequential initial vaccination and revaccinations with PPSV23

Initial administration of sequential vaccination instead of PPSV23 in the 2016-2030 period could prevent an additional 531-950 IPD episodes, 2285-2985 Pnc-CAPin episodes and 134-282 disease-related deaths in the 60+ age group, depending on the frequency of vaccination and age at initial vaccination. The most effective of the analyzed strategies is sequential initial vaccination at age 60 with revaccination every six years (see Figure 43).

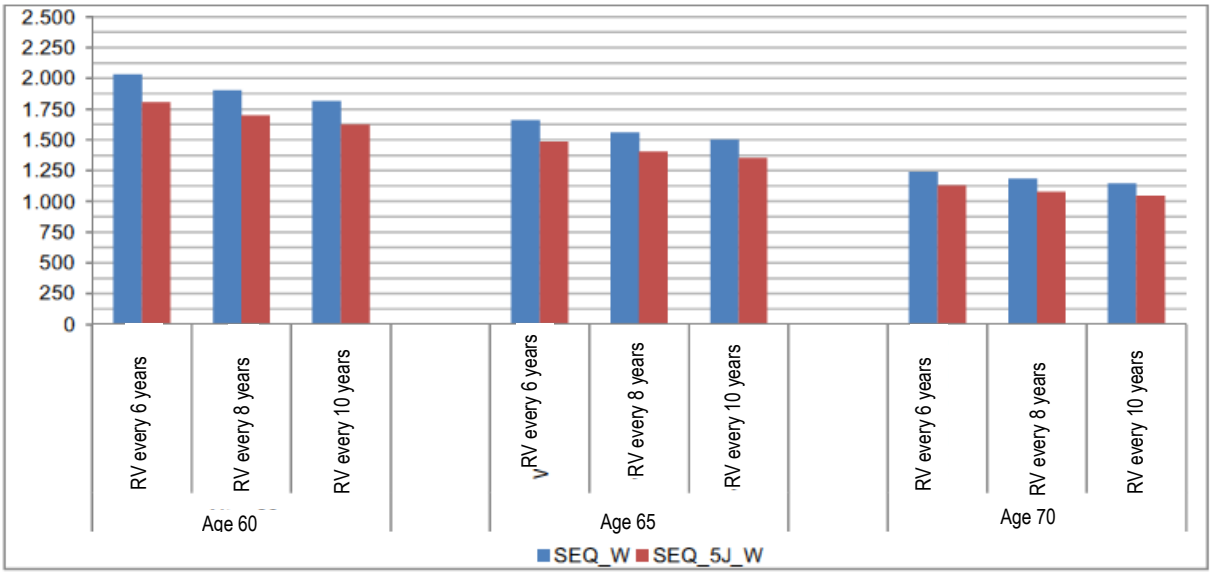
Figure 43: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A4: Additionally prevented cases



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one dose of PCV13 + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

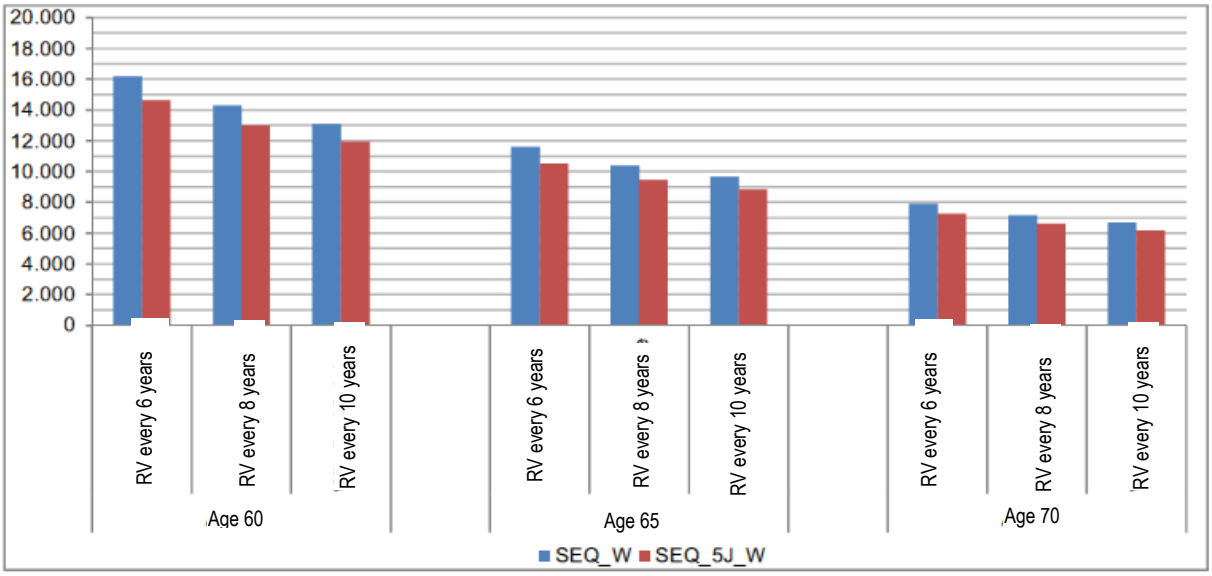
This vaccination strategy however provides the smallest effectiveness gain versus revaccination with initial PPSV23 vaccination as the higher effectiveness of sequential vaccination is due in particular to the longer duration of immunity with PCV13. This benefit of sequential vaccination is lost in large part with revaccination after six years unless the effectiveness of revaccination falls below a certain threshold. (see Figure 44 and 45). This is not the case in the presence of 25% lower effectiveness of revaccinations with PPSV23, so a graph has not been provided (but see Tables 17, 20 and 21 on incremental cost effectiveness).

Figure 44: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A4: NNV to prevent one additional hospitalization



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one dose of PCV13 + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

Figure 45: Vaccination strategy SEQ_W/SEQ_5J_W vs. PPSV23_W - Scenario A4: NNV to prevent one additional death



PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one dose of PCV13 + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **Age:** Age at initial vaccination; **RV:** revaccination

3.3.4.2 Health economics results

3.3.4.2.1 Initial vaccination with PPSV23 and revaccinations with PPSV23

The results are as given for Scenario A3 as the PPSV23 parameters are the same as for Scenario A3.

3.3.4.2.2 Sequential initial vaccination and revaccinations with PPSV23

If PPSV23 revaccination is as effective as initial PPSV23 vaccination, then the incremental cost effectiveness ratio is EUR 71,871-101,814 per QALY gained, depending on age at initial vaccination and frequency of revaccination. The incremental cost effectiveness ratio rises with reduction of the interval between initial vaccination and revaccination. If revaccination is 25% less effective than the initial vaccination, then the additional cost per gained QALY of the strategies with sequential initial vaccination declines marginally or remains constant.

Table 20: Vaccination strategy SEQ_W vs. PPSV23_W - Scenario A4: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 101,814	EUR 91,293	EUR 84,962
65	EUR 90,201	EUR 81,833	EUR 77,441
70	EUR 82,643	EUR 75,687	EUR 71,871
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 97,193	EUR 90,573	EUR 84,962
65	EUR 86,736	EUR 81,323	EUR 77,441
70	EUR 79,731	EUR 75,264	EUR 71,871

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_W:** Sequential initial vaccination with one PCV13 dose + PPSV23 booster six months later + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

Table 21: Vaccination strategy SEQ_5J_W vs. PPSV23_W - Scenario A4: Incremental cost effectiveness (additional cost per QALY gained)

Vaccination age	Revaccination every 6 years	Revaccination every 8 years	Revaccination every 10 years
Effectiveness of revaccination: 100% of initial vaccination			
60	EUR 91,544	EUR 82,488	EUR 76,977
65	EUR 81,368	EUR 74,127	EUR 70,291
70	EUR 75,124	EUR 69,039	EUR 65,677
Effectiveness of revaccination: 75% of initial vaccination			
60	EUR 87,558	EUR 81,862	EUR 76,977
65	EUR 78,363	EUR 73,682	EUR 70,291
70	EUR 72,572	EUR 68,667	EUR 65,677

PPSV23_W: Initial vaccination with PPSV23 + lifelong revaccinations with PPSV23 at specified intervals; plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period; **SEQ_5J_W:** Sequential initial vaccination in the 2016-2020 period/initial vaccination with PPSV23 in the 2021-2030 period + lifelong revaccinations with PPSV23 at specified intervals, plus revaccinations with PPSV23 for individuals who received the initial vaccination in the 1996-2015 period

3.4 Short-term results (initial vaccination in the 2016-2020 period)

Tables 22-25 show the results for individuals reaching the defined vaccination age in the 2016-2020 period (lifelong follow-up). The strategies involving revaccination only include cohorts who received the initial vaccination in the 2016-2020 period.

Table 22: Short-term results, Scenario A1: PPSV23 effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 and PCV13

	Prevented cases (lifelong cumulative)			**NNV* to prevent one**		**Cost per prevented hospitali-zation*** **	**Cost per quality adjusted life year gained (QALY)**
Vaccine/ Vaccination age	Pnc-CAPin**	IPD	Deaths	Hospitali-zation***	Death		
PPSV23 vs. no vaccination							
60 years	1,505	748	270	801	6,690	EUR 18,838	EUR 14,383
65 years	1,440	700	298	725	5,208	EUR 19,634	EUR 15,670
70 years	1,357	627	303	648	4,247	EUR 17,056	EUR 15,436
PCV13 vs. no vaccination							
60 years	454	271	101	2,490	17,931	EUR 149,338	EUR 112,606
65 years	463	265	119	2,134	13,026	EUR 129,327	EUR 100,829
70 years	519	236	137	1,703	9,411	EUR 102,370	EUR 96,372
Sequential vaccination vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
60 years	186	110	47	6,072	38,024	EUR 375,498	EUR 366,499
65 years	212	113	56	4,762	27,438	EUR 293,721	EUR 318,812
70 years	273	90	71	3,521	17,960	EUR 216,506	EUR 306,411
Initial vaccination with PPSV23 at the age of 60 years + revaccinations with PPSV23 vs. no vaccination							
every 6 years	17,898	4,271	4,272	398	2,064	EUR 6,690	EUR 12,839
every 8 years	13,734	3,424	3,267	396	2,077	EUR 6,685	EUR 12,294
every 10 years	11,026	2,826	2,650	403	2,104	EUR 6,880	EUR 12,195
Sequential vaccination at the age of 60 years + revaccinations withPPSV23 vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
every 6 years	47	24	11	25,038	167,139	EUR 1,561,739	EUR 2,810,187
every 8 years	120	70	29	9,471	61,333	EUR 587,983	EUR 598,592
every 10 years	160	95	40	7,052	45,011	EUR 436,714	EUR 425,785

*Number needed to vaccinate; **hospitalized Pnc-CAP; *** Pnc-CAP or IPD

Table 23: Short-term results, Scenario A2: PPSV23 effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 only with PPSV23

	Prevented cases (lifelong cumulative)			NNV* to prevent one		Cost per prevented hospitali-zation***	Cost per quality adjusted life year gained (QALY)
Vaccine/ Vaccination age	Pnc-CAPin**	IPD	Deaths	Hospitali-zation***	Death		
PPSV23 vs. no vaccination							
60 years	1,505	748	270	801	6,690	EUR 18,838	EUR 14,383
65 years	1,440	700	298	725	5,208	EUR 19,634	EUR 15,670
70 years	1,357	627	303	648	4,247	EUR 17,056	EUR 15,436
PCV13 vs. no vaccination							
60 years	813	485	188	1,391	9,613	EUR 80,499	EUR 59,102
65 years	841	480	221	1,175	7,029	EUR 69,128	EUR 53,717
70 years	962	430	256	924	5,014	EUR 53,584	EUR 50,582
Sequential vaccination vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
60 years	502	324	130	2,175	13,788	EUR 130,323	EUR 101,032
65 years	546	327	153	1,768	10,077	EUR 106,065	EUR 90,647
70 years	672	284	186	1,335	6,870	EUR 79,447	EUR 85,310
Initial vaccination with PPSV23 at the age of 60 years + revaccinations with PPSV23 vs. no vaccination							
every 6 years	17,898	4,271	4,272	398	2,064	EUR 6,690	EUR 12,839
every 8 years	13,734	3,424	3,267	396	2,077	EUR 6,685	EUR 12,294
every 10 years	11,026	2,826	2,650	403	2,104	EUR 6,880	EUR 12,195
Sequential vaccination at the age of 60 years + revaccinations withPPSV23 vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
every 6 years	246	183	66	4,191	27,101	EUR 255,020	EUR 179,637
every 8 years	372	246	95	2,910	18,913	EUR 175,743	EUR 129,773
every 10 years	450	294	116	2,415	15,533	EUR 145,118	EUR 109,942

*Number needed to vaccinate; **hospitalized Pnc-CAP; *** Pnc-CAP or IPD

Table 24: Short-term results, Scenario A3: PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 with PPSV23 and PCV13

	Prevented cases (lifelong cumulative)			NNV* to prevent one		Cost per prevented hospitali-zation***	Cost per quality adjusted life year gained (QALY)
Vaccine/ vaccination age	Pnc-CAPin**	IPD	Deaths	Hospitali-zation***	Death		
PPSV23 vs. no vaccination							
60 years	0	748	128	2,413	14,063	EUR 72,085	EUR 37,746
65 years	0	700	146	2,217	10,627	EUR 67,244	EUR 36,344
70 years	0	627	144	2,051	8,903	EUR 61,403	EUR 37,549
PCV13 vs. no vaccination							
60 years	454	271	101	2,490	17,931	EUR 149,338	EUR 112,606
65 years	463	265	119	2,134	13,026	EUR 129,327	EUR 100,829
70 years	519	236	137	1,703	9,411	EUR 102,370	EUR 96,372
Sequential vaccination vs. PPSV23 (*additionally* preventable cases and *additionally* required vaccinations with PCV13 versus vaccination with PPSV23 alone)							
60 years	454	110	72	3,187	24,889	EUR 192,859	EUR 178,595
65 years	463	113	83	2,684	18,681	EUR 163,898	EUR 163,370
70 years	519	90	99	2,098	12,854	EUR 127,421	EUR 153,893
Initial vaccination with PPSV23 at the age of 60 years + revaccinations with PPSV23 vs. no vaccination							
every 6 years	0	4,271	1,359	2,064	6,485	EUR 43,657	EUR 40,730
every 8 years	0	3,424	1,076	1,982	6,308	EUR 42,600	EUR 38,642
every 10 years	0	2,826	868	1,974	6,426	EUR 43,186	EUR 38,338
Sequential vaccination at the age of 60 years + revaccinations withPPSV23 vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
every 6 years	454	24	66	3,761	27,087	EUR 234,936	EUR 247,730
every 8 years	454	70	77	3,433	23,262	EUR 213,880	EUR 207,647
every 10 years	454	95	84	3,275	21,472	EUR 203,719	EUR 191,253

*Number needed to vaccinate; **hospitalized Pnc-CAP; *** Pnc-CAP or IPD

Table 25: Short-term results, Scenario A4: PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 only with PPSV23

	prevented cases (lifelong cumulative)			NNV* to prevent one		Cost per prevented hospitali-zation***	Cost per quality adjusted life year gained (QALY)
Vaccine/ Vaccination age	Pnc-CAPin**	IPD	Deaths	Hospitali-zation***	Death		
PPSV23 vs. no vaccination							
60 years	0	748	128	2,413	14,063	EUR 72,085	EUR 37,746
65 years	0	700	146	2,217	10,627	EUR 67,244	EUR 36,344
70 years	0	627	144	2,051	8,903	EUR 61,403	EUR 37,549
PCV13 vs. no vaccination							
60 years	813	485	188	1,391	9,613	EUR 80,499	EUR 59,102
65 years	841	480	221	1,175	7,029	EUR 69,128	EUR 53,717
70 years	962	430	256	924	5,014	EUR 53,584	EUR 50,582
Sequential vaccination vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
60 years	813	324	159	1,582	11,287	EUR 92,372	EUR 74,203
65 years	841	327	184	1,321	8,379	EUR 78,315	EUR 68,106
70 years	962	284	219	1,024	5,824	EUR 60,081	EUR 63,604
Initial vaccination with PPSV23 at the age of 60 years + revaccinations with PPSV23 vs. no vaccination							
every 6 years	0	4,271	1,359	2,064	6,485	EUR 43,657	EUR 40,730
every 8 years	0	3,424	1,076	1,982	6,308	EUR 42,600	EUR 38,642
every 10 years	0	2,826	868	1,974	6,426	EUR 43,186	EUR 38,338
Sequential vaccination at the age of 60 years + revaccinations with PPSV23 vs. PPSV23 (*additionally preventable cases and additionally required vaccinations with PCV13 versus vaccination with PPSV23 alone*)							
every 6 years	813	183	123	1,806	14,642	EUR 106,436	EUR 91,544
every 8 years	813	246	138	1,699	13,000	EUR 99,677	EUR 82,488
every 10 years	813	294	151	1,625	11,927	EUR 95,051	EUR 76,977

*Number needed to vaccinate; **hospitalized Pnc-CAP; *** Pnc-CAP or IPD

4 Conclusions

In all four scenarios studied, sequential vaccination of the 60+ population prevents the largest number of Pnc infections and deaths. Depending on scenario and vaccination age, short-term analysis (vaccination in the 2016-2020 period only) indicates that sequential vaccination prevents an additional 90-327 IPD cases, 186-962 noninvasive Pnc cases and 47-219 deaths (cumulative over the lifetime of vaccination recipients) compared with the PPSV23 vaccination strategy.

The resources required with combined vaccination (PCV13 + PPSV23) to prevent one additional hospitalization or one additional disease-related death versus vaccination with PPSV23 on its own are relatively high, however. The NNVs to prevent one hospitalization or one death are smaller than for PPSV23 only if PPSV23 is ineffective against noninvasive Pnc-CAP and PCV13 is as effective against serotype 3 as against the other PCV13 serotypes (assumption for PPSV23: only half as effective as against the other PPSV23 serotypes). Given the higher price of the PCV13 vaccine, vaccination with PPSV23 on its own would still be the preferred option from an economics point of view (approx. EUR36,000-38,000 / QALY vs. EUR77,000-92,000per QALY).

In Scenarios A1-A3, PPSV23 saves costs and is more effective (in terms of years of life and QALYs gained) than vaccination with PCV13 on its own. In Scenario A4 (PPSV23 not effective against noninvasive Pnc-CAP / reduced effectiveness against serotype 3 only with PPSV23), vaccination with PCV13 on its own is more effective. From the point of view of cost effectiveness, PPSV23 would be preferable in this scenario too.

Assuming that vaccine effectiveness does not depend on age at vaccination, immunization strategies become more efficient as the age at vaccination increases, in terms of the number of vaccinations needed to prevent one hospitalization or one disease-related death. Consequently, strategies

involving revaccinations are not only more effective (in preventing additional Pnc infections and deaths) but also more efficient with regard to the NNVs to prevent one hospitalization or one death than single, one-off vaccinations, provided the interval between revaccinations is long enough. This still applies if the effectiveness of revaccinations is 25% lower than that of the initial vaccinations. The most effective vaccination strategy of all the strategies studied is repeated immunization every six years, with the initial vaccination taking place at the age of 60. Any losses of efficiency versus other revaccination strategies are marginal. From the point of view of efficiency, initial vaccination with PPSV23 would be preferable to sequential initial vaccination.

It should be noted that the results presented here are based on the assumption that the incidence of serotype 3 will persist at the level of the 2013/2014 Pnc season. If pediatric vaccination eventually also eliminates serotype 3 (albeit with some delay versus the other PCV13 serotypes), then vaccination of the 60+ population with PCV13 alone, and sequential vaccination, would have to be rejected based on considerations of efficiency.

References

1. Kupronis, B.A., Richards, C.L., Whitney, C.G.: Invasive pneumococcal disease in older adults residing in long-term care facilities and in the community. Journal of the American Geriatrics Society 51(11), 1520–1525 (2003)
2. Lencastre, H. de, Kristinsson, K.G., Brito-Avô, A., Sanches, I.S., Sá-Leão, R., Saldanha, J., Sigvaldadottir, E., Karlsson, S., Oliveira, D., Mato, R., Aires de Sousa, M, Tomasz, A.: Carriage of respiratory tract pathogens and molecular epidemiology of Streptococcus pneumoniae colonization in healthy children attending day care centers in Lisbon, Portugal. Microbial drug resistance (Larchmont, N.Y.) 5(1), 19–29 (1999)
3. Hussain, M., Melegaro, A., Pebody, R.G., George, R., Edmunds, W.J., Talukdar, R., Martin, S.A., Efstratiou, A., Miller, E.: A longitudinal household study of Streptococcus pneumoniae nasopharyngeal carriage in a UK setting. Epidemiology and infection 133(5), 891–898 (2005). doi: 10.1017/S0950268805004012
4. Leino, T., Hoti, F., Syrjänen, R., Tanskanen, A., Auranen, K.: Clustering of serotypes in a longitudinal study of Streptococcus pneumoniae carriage in three day care centres. BMC Infect Dis 8(1), 173 (2008). doi: 10.1186/1471-2334-8-173
5. Welte, T., Torres, A., Nathwani, D.: Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax 67(1), 71–79 (2012). doi: 10.1136/thx.2009.129502
6. Robert Koch Institut: Pneumokokken-Polysaccharid-Impfung – Anpassung der Empfehlung und Begründung. Epidemiologisches Bulletin(32), 337–338 (2009)
7. Robert Koch Institut: Stellungnahme zur Impfung Erwachsener gegen Pneumokokken. Epidemiologisches Bulletin(7), 55–56 (2012)
8. Robert Koch Institut: Standardimpfungen des Erwachsenenalters, Indikations- und Auffrischimpfungen sowie Impfungen aufgrund eines erhöhten beruflichen Risikos oder aufgrund einer Reise. Epidemiologisches Bulletin(34), 330–344 (2015)
9. Loo, J.D., Conklin, L., Fleming-Dutra, K.E., Knoll, M.D., Park, D.E., Kirk, J., Goldblatt, D., O'Brien, K.L., Whitney, C.G.: Systematic review of the indirect effect of pneumococcal conjugate vaccine dosing schedules on pneumococcal disease and colonization. The Pediatric infectious disease journal 33 Suppl 2, S161-71 (2014). doi: 10.1097/INF.0000000000000084
10. Rodenburg, G.D., Greeff, S.C. de, Jansen, Angelique G C S, Melker, H.E. de, Schouls, L.M., Hak, E., Spanjaard, L., Sanders, E.A.M., van der Ende, A.: Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. Emerging infectious diseases 16(5), 816–823 (2010). doi: 10.3201/eid1605.091223
11. Vestrheim, D.F., Høiby, E.A., Bergsaker, M.R., Rønning, K., Aaberge, I.S., Caugant, D.A.: Indirect effect of conjugate pneumococcal vaccination in a 2+1 dose schedule. Vaccine 28(10), 2214–2221 (2010). doi: 10.1016/j.vaccine.2009.12.054
12. Harboe, Z.B., Valentiner-Branth, P., Benfield, T.L., Christensen, J.J., Andersen, P.H., Howitz, M., Krogfelt, K.A., Lambertsen, L., Konradsen, H.B.: Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme. Vaccine 28(14), 2642–2647 (2010). doi: 10.1016/j.vaccine.2010.01.017
13. Pilishvili, T., Lexau, C., Farley, M.M., Hadler, J., Harrison, L.H., Bennett, N.M., Reingold, A., Thomas, A., Schaffner, W., Craig, A.S., Smith, P.J., Beall, B.W., Whitney, C.G., Moore, M.R.: Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. The Journal of infectious diseases 201(1), 32–41 (2010). doi: 10.1086/648593
14. Weinberger, D.M., Malley, R., Lipsitch, M.: Serotype replacement in disease after pneumococcal vaccination. The Lancet 378(9807), 1962–1973 (2011). doi: 10.1016/S0140-6736(10)62225-8
15. van der Linden, M., Weiß, S., Falkenhorst, G., Siedler, A., Imöhl, M., Kries, R. von: Four years of universal pneumococcal conjugate infant vaccination in Germany: impact on incidence of invasive pneumococcal disease and serotype distribution in children. Vaccine 30(40), 5880–5885 (2012). doi: 10.1016/j.vaccine.2012.06.068

16. Rückinger, S., van der Linden, M., Reinert, R.R., Kries, R. von, Burckhardt, F., Siedler, A.: Reduction in the incidence of invasive pneumococcal disease after general vaccination with 7-valent pneumococcal conjugate vaccine in Germany. Vaccine 27(31), 4136–4141 (2009). doi: 10.1016/j.vaccine.2009.04.057
17. Moore, M.R., Link-Gelles, R., Schaffner, W., Lynfield, R., Lexau, C., Bennett, N.M., Petit, S., Zansky, S.M., Harrison, L.H., Reingold, A., Miller, L., Scherzinger, K., Thomas, A., Farley, M.M., Zell, E.R., Taylor, T.H., Pondo, T., Rodgers, L., McGee, L., Beall, B., Jorgensen, J.H., Whitney, C.G.: Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA. Analysis of multisite, population-based surveillance. The Lancet Infectious Diseases 15(3), 301–309 (2015). doi: 10.1016/S1473-3099(14)71081-3
18. Rodrigo, C., Bewick, T., Sheppard, C., Greenwood, S., Mckeever, T.M., Trotter, C.L., Slack, M., George, R., Lim, W.S.: Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. The European respiratory journal 45(6), 1632–1641 (2015). doi: 10.1183/09031936.00183614
19. Tin Tin Htar, M., Christopoulou, D., Schmitt, H.-J.: Pneumococcal serotype evolution in Western Europe. BMC infectious diseases 15, 419 (2015). doi: 10.1186/s12879-015-1147-x
20. Steens, A., Vestrheim, D.F., Blasio, B.F. de: Pneumococcal vaccination in older adults in the era of childhood vaccination: Public health insights from a Norwegian statistical prediction study. Epidemics 11, 24–31 (2015). doi: 10.1016/j.epidem.2015.01.001
21. Harboe, Z.B., Dalby, T., Weinberger, D.M., Benfield, T., Mølbak, K., Slotved, H.C., Suppli, C.H., Konradsen, H.B., Valentiner-Branth, P.: Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 59(8), 1066–1073 (2014). doi: 10.1093/cid/ciu524
22. van der Linden, M., Falkenhorst, G., Perniciaro, S., Imöhl, M.: Effects of Infant Pneumococcal Conjugate Vaccination on Serotype Distribution in Invasive Pneumococcal Disease among Children and Adults in Germany. PLoS ONE 10(7), e0131494 (2015). doi: 10.1371/journal.pone.0131494
23. Weiss, S., Falkenhorst, G., van der Linden, M, Imohl, M., Kries, R. von: Impact of 10- and 13-valent pneumococcal conjugate vaccines on incidence of invasive pneumococcal disease in children aged under 16 years in Germany, 2009 to 2012. Euro surveillance : bulletin Européen sur les maladies transmissibles = European communicable disease bulletin 20(10), 21057 (2015)
24. Waight, P.A., Andrews, N.J., Ladhani, S.N., Sheppard, C.L., Slack, M.P.E., Miller, E.: Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. The Lancet. Infectious diseases 15(5), 535–543 (2015). doi: 10.1016/S1473-3099(15)70044-7
25. Andrews, N.J., Waight, P.A., Burbidge, P., Pearce, E., Roalfe, L., Zancolli, M., Slack, M., Ladhani, S.N., Miller, E., Goldblatt, D.: Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. The Lancet. Infectious diseases 14(9), 839–846 (2014). doi: 10.1016/S1473-3099(14)70822-9
26. Bonten, M.J., Huijts, S.M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., van Werkhoven, C.H., van Deursen, A.M., Sanders, E.A., Verheij, T.J., Patton, M., McDonough, A., Moradoghli-Haftvani, A., Smith, H., Mellelieu, T., Pride, M.W., Crowther, G., Schmoele-Thoma, B., Scott, D.A., Jansen, K.U., Lobatto, R., Oosterman, B., Visser, N., Caspers, E., Smorenburg, A., Emini, E.A., Gruber, W.C., Grobbee, D.E.: Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. N Engl J Med 372(12), 1114–1125 (2015). doi: 10.1056/NEJMoa1408544
27. Rudnick, W., Liu, Z., Shigayeva, A., Low, D.E., Green, K., Plevneshi, A., Devlin, R., Downey, J., Katz, K., Kitai, I., Krajden, S., Ostrowska, K., Richardson, D., Richardson, S., Sarabia, A., Silverman, M., Simor, A.E., Tyrrell, G., McGeer, A.: Pneumococcal vaccination programs and the burden of invasive pneumococcal disease in Ontario, Canada, 1995-2011. Vaccine 31(49), 5863–5871 (2013). doi: 10.1016/j.vaccine.2013.09.049

28. Ogilvie, I., Khoury, A.E., Cui, Y., Dasbach, E., Grabenstein, J.D., Goetghebeur, M.: Cost-effectiveness of pneumococcal polysaccharide vaccination in adults: a systematic review of conclusions and assumptions. Vaccine 27(36), 4891–4904 (2009). doi: 10.1016/j.vaccine.2009.05.061

29. Jiang, Y., Gauthier, A., Keeping, S., Carroll, S.: Cost-effectiveness of vaccinating the elderly and at-risk adults with the 23-valent pneumococcal polysaccharide vaccine or 13-valent pneumococcal conjugate vaccine in the UK. Expert review of pharmacoeconomics & outcomes research 14(6), 913–927 (2014). doi: 10.1586/14737167.2014.950232

30. Jiang, Y., Gauthier, A., Annemans, L., van der Linden, M., Nicolas-Spony, L., Bresse, X.: Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. Expert review of pharmacoeconomics & outcomes research 12(5), 645–660 (2012). doi: 10.1586/erp.12.54

31. Grzesiowski, P., Aguiar-Ibáñez, R., Kobryń, A., Durand, L., Puig, P.-E.: Cost-effectiveness of polysaccharide pneumococcal vaccination in people aged 65 and above in Poland. Human vaccines & immunotherapeutics 8(10), 1382–1394 (2012). doi: 10.4161/hv.21571

32. Smith, K.J., Wateska, A.R., Nowalk, M.P., Raymund, M., Nuorti, J.P., Zimmerman, R.K.: Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA 307(8), 804–812 (2012). doi: 10.1001/jama.2012.169

33. Chen, J., O'Brien, M.A., Yang, H.K., Grabenstein, J.D., Dasbach, E.J.: Cost-effectiveness of pneumococcal vaccines for adults in the United States. Advances in therapy 31(4), 392–409 (2014). doi: 10.1007/s12325-014-0115-y

34. Soárez, P.C. de, Sartori, A.M.C., Freitas, A.C., Nishikawa, Á.M., Novaes, H.M.D.: Cost-Effectiveness Analysis of Universal Vaccination of Adults Aged 60 Years with 23-Valent Pneumococcal Polysaccharide Vaccine versus Current Practice in Brazil. PLoS ONE 10(6), e0130217 (2015). doi: 10.1371/journal.pone.0130217

35. Dirmesropian, S., Wood, J.G., MacIntyre, C.R., Newall, A.T.: A review of economic evaluations of 13-valent pneumococcal conjugate vaccine (PCV13) in adults and the elderly. Human vaccines & immunotherapeutics 11(4), 818–825 (2015). doi: 10.1080/21645515.2015.1011954

36. Rozenbaum, M.H., van Hoek, A.J., Fleming, D., Trotter, C.L., Miller, E., Edmunds, W.J.: Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ (Clinical research ed.) 345, e6879 (2012). doi: 10.1136/bmj.e6879

37. Pradas, R., Gil de Miguel, A., Álvaro, A., Gil-Prieto, R., Lorente, R., Méndez, C., Guijarro, P., Antoñanzas, F.: Budget impact analysis of a pneumococcal vaccination programme in the 65-year-old Spanish cohort using a dynamic model. BMC infectious diseases 13, 175 (2013). doi: 10.1186/1471-2334-13-175

38. Liguori, G., Parlato, A., Zamparelli, A.S., Belfiore, P., Gallé, F., Di Onofrio, V., Riganti, C., Zamparelli, B.: Adult immunization with 13-valent pneumococcal vaccine in Campania region, South Italy: an economic evaluation. Human vaccines & immunotherapeutics 10(2), 492–497 (2014). doi: 10.4161/hv.26888

39. Rozenbaum, M.H., Hak, E., van der Werf, Tjip S, Postma, M.J.: Results of a cohort model analysis of the cost-effectiveness of routine immunization with 13-valent pneumococcal conjugate vaccine of those aged or =65 years in the Netherlands. Clinical Therapeutics 32(8), 1517–1532 (2010). doi: 10.1016/j.clinthera.2010.06.016

40. Boccalini, S., Bechini, A., Levi, M., Tiscione, E., Gasparini, R., Bonanni, P.: Cost-effectiveness of new adult pneumococcal vaccination strategies in Italy. Human vaccines & immunotherapeutics 9(3), 699–706 (2013)

41. Cho, B.-H., Stoecker, C., Link-Gelles, R., Moore, M.R.: Cost-effectiveness of administering 13-valent pneumococcal conjugate vaccine in addition to 23-valent pneumococcal polysaccharide vaccine to adults with immunocompromising conditions. Vaccine 31(50), 6011–6021 (2013). doi: 10.1016/j.vaccine.2013.10.024

42. Smith, K.J., Nowalk, M.P., Raymund, M., Zimmerman, R.K.: Cost-effectiveness of pneumococcal conjugate vaccination in immunocompromised adults. Vaccine 31(37), 3950–3956 (2013). doi: 10.1016/j.vaccine.2013.06.037

43. Weycker, D., Sato, R., Strutton, D., Edelsberg, J., Atwood, M., Jackson, L.A.: Public health and economic impact of 13-valent pneumococcal conjugate vaccine in US adults aged ≥50 years. Vaccine 30(36), 5437–5444 (2012). doi: 10.1016/j.vaccine.2012.05.076

44. Smith, K.J., Wateska, A.R., Nowalk, M.P., Raymund, M., Lee, B.Y., Zimmerman, R.K.: Modeling of cost effectiveness of pneumococcal conjugate vaccination strategies in U.S. older adults. American journal of preventive medicine 44(4), 373–381 (2013). doi: 10.1016/j.amepre.2012.11.035

45. Rodríguez-GonzálezMoro, J.M., Menendez, R., Campins, M., Lwoff, N., Oyagüez, I., Echave, M., Rejas, J., Antoñanzas, F.: Cost-Effectiveness Of A 13-Valent Conjugate Pneumococcal Vaccination Program In Copd Patients Aged 50+ Years In Spain. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 18(7), A502 (2015). doi: 10.1016/j.jval.2015.09.1424

46. Hoshi, S.-I., Kondo, M., Okubo, I.: Economic Evaluation of Immunisation Programme of 23-Valent Pneumococcal Polysaccharide Vaccine and the Inclusion of 13-Valent Pneumococcal Conjugate Vaccine in the List for Single-Dose Subsidy to the Elderly in Japan. PLoS ONE 10(10), e0139140 (2015). doi: 10.1371/journal.pone.0139140

47. Mangen, M.-J.J., Rozenbaum, M.H., Huijts, S.M., van Werkhoven, C.H., Postma, D.F., Atwood, M., van Deursen, Anna M M, van der Ende, A., Grobbee, D.E., Sanders, E.A.M., Sato, R., Verheij, T.J.M., Vissink, C.E., Bonten, M.J.M., Wit, G.A. de: Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. The European respiratory journal 46(5), 1407–1416 (2015). doi: 10.1183/13993003.00325-2015

48. Kuhlmann, A., Theidel, U., Pletz, M.W., von der Schulenburg, J-Matthias Graf: Potential cost-effectiveness and benefit-cost ratios of adult pneumococcal vaccination in Germany. Health economics review 2(1), 4 (2012). doi: 10.1186/2191-1991-2-4

49. Mossong, J., Hens, N., Jit, M., Beutels, P., Auranen, K., Mikolajczyk, R., Massari, M., Salmaso, S., Tomba, G.S., Wallinga, J., Heijne, J., Sadkowska-Todys, M., Rosinska, M., Edmunds, W.J.: Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases. Plos Med 5(3), e74 (2008). doi: 10.1371/journal.pmed.0050074

50. Choi, Y.H., Jit, M., Gay, N., Andrews, N., Waight, P.A., Melegaro, A., George, R., Miller, E., Borrow, R.: 7-Valent Pneumococcal Conjugate Vaccination in England and Wales: Is It Still Beneficial Despite High Levels of Serotype Replacement? PLoS ONE 6(10), e26190 (2011). doi: 10.1371/journal.pone.0026190

51. Melegaro, A., Choi, Y., George, R., Edmunds, W.J., Miller, E., Gay, N.J.: Dynamic models of pneumococcal carriage and the impact of the Heptavalent Pneumococcal Conjugate Vaccine on invasive pneumococcal disease. BMC Infect Dis 10(1), 90 (2010). doi: 10.1186/1471-2334-10-90

52. Auranen, K., Mehtala, J., Tanskanen, A., S. Kaltoft, M.: Between-Strain Competition in Acquisition and Clearance of Pneumococcal Carriage—Epidemiologic Evidence From a Longitudinal Study of Day-Care Children. American Journal of Epidemiology 171(2), 169–176 (2009). doi: 10.1093/aje/kwp351

53. Flasche, S., van Hoek, A.J., Sheasby, E., Waight, P., Andrews, N., Sheppard, C., George, R., Miller, E., Klugman, K.P.: Effect of Pneumococcal Conjugate Vaccination on Serotype-Specific Carriage and Invasive Disease in England: A Cross-Sectional Study. Plos Med 8(4), e1001017 (2011). doi: 10.1371/journal.pmed.1001017

54. van Hoek, A.J., Sheppard, C.L., Andrews, N.J., Waight, P.A., Slack, M.P.E., Harrison, T.G., Ladhani, S.N., Miller, E.: Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine 32(34), 4349–4355 (2014). doi: 10.1016/j.vaccine.2014.03.017

55. Brueggemann, A.B., Griffiths, D.T., Meats, E., Peto, T., Crook, D.W., Spratt, B.G.: Clonal relationships between invasive and carriage Streptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. The Journal of infectious diseases 187(9), 1424–1432 (2003). doi: 10.1086/374624

56. Trotter, C.L., Waight, P., Andrews, N.J., Slack, M., Efstratiou, A., George, R., Miller, E.: Epidemiology of invasive pneumococcal disease in the pre-conjugate vaccine era: England and Wales, 1996–2006. Journal of Infection 60(3), 200–208 (2010). doi: 10.1016/j.jinf.2009.12.008

57. Choi, Y.H., Jit, M., Flasche, S., Gay, N., Miller, E., Beall, B.: Mathematical Modelling Long-Term Effects of Replacing Prevnar7 with Prevnar13 on Invasive Pneumococcal Diseases in England and Wales. PLoS ONE 7(7), e39927 (2012). doi: 10.1371/journal.pone.0039927

58. Högberg, L., Geli, P., Ringberg, H., Melander, E., Lipsitch, M., Ekdahl, K.: Age- and serogroup-related differences in observed durations of nasopharyngeal carriage of penicillin-resistant pneumococci. Journal of clinical microbiology 45(3), 948–952 (2007). doi: 10.1128/JCM.01913-06

59. von Kries, R. von, Toschke, A.M., Siedler, A.: Population-based Nationwide Study on Invasive Pneumococcal Infections among Children in Germany (1997-2003) (unpublished) (2005)

60. Reinert, R.R., Haupts, S., van der Linden, M, Heeg, C., Cil, M.Y., Al-Lahham, A., Fedson, D.S.: Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001-2003. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 11(12), 985–991 (2005). doi: 10.1111/j.1469-0691.2005.01282.x

61. Statistisches Bundesamt: Diagnosedaten der Krankenhäuser ab 2000 (2014)

62. IMS Health Deutschland: Verschreibungsindex für Pharmazeutika (VIP) (unpublished) (2009)

63. Rozenbaum, M.H., Pechlivanoglou, P., van der Werf, T S, Lo-Ten-Foe, J.R., Postma, M.J., Hak, E.: The role of Streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 32(3), 305–316 (2013). doi: 10.1007/s10096-012-1778-4

64. van Hoek, A.J., Andrews, N., Waight, P.A., George, R., Miller, E., Aguilar, L.: Effect of Serotype on Focus and Mortality of Invasive Pneumococcal Disease: Coverage of Different Vaccines and Insight into Non-Vaccine Serotypes. PLoS ONE 7(7), e39150 (2012). doi: 10.1371/journal.pone.0039150

65. Poethko-Muller, C., Schmitz, R.: Vaccination coverage in German adults: results of the German Health Interview and Examination Survey for Adults (DEGS1) (Impfstatus von Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1)). Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 56(5-6), 845–857 (2013). doi: 10.1007/s00103-013-1693-6

66. Falkenhorst, G., Remschmidt, C., Harder, T., Hummers-Pradier, E., Wichmann, O., Bogdan, C.: Wirksamkeit des 23-valenten Pneumokokken-Polysaccharidimpfstoffs bei Senioren: systematische Literaturübersicht und Meta-Analyse. Im Review.

67. Ochoa-Gondar, O., Vila-Corcoles, A., Rodriguez-Blanco, T., Gomez-Bertomeu, F., Figuerola-Massana, E., Raga-Luria, X., Hospital-Guardiola, I.: Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine Against Community-Acquired Pneumonia in the General Population Aged >=60 Years: 3 Years of Follow-up in the CAPAMIS Study. Clinical Infectious Diseases 58(7), 909–917 (2014). doi: 10.1093/cid/ciu002

68. Melegaro, A., Edmunds, W.J.: The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. European journal of epidemiology 19(4), 365–375 (2004)

69. Braun, S., Prenzler, A., Mittendorf, T., Schulenburg, J.M.v.d.: Bewertung von Ressourcenverbräuchen im deutschen Gesundheitswesen aus Sicht der Gesetzlichen Krankenversicherung. Gesundheitswesen 71(01), 19–23 (2009). doi: 10.1055/s-0028-1102930

70. Lauertaxe: Arzneimittelpreise (2014)

71. Institut für das Entgeltsystem im Krankenhaus GmbH: G-DRG-System 2014, Reportbrowser 2012/2014 (2014)

72. Kassenärztliche Bundesvereinigung: Einheitlicher Bewertungsmaßstab (EBM) 2014

73. Bundesagentur für Arbeit: Analyse der gemeldeten Arbeitsstellen (2013)

74. Statistisches Bundesamt: VGR des Bundes - Bruttonationaleinkommen, Volkseinkommen (2014)

75. Statistisches Bundesamt: Bevölkerung, Erwerbstätige, Erwerbslose, Erwerbspersonen, Nichterwerbspersonen: Deutschland, Jahre, Altersgruppen (2014)

76. Gesundheitsberichterstattung des Bundes: Arbeitsunfähigkeit bei AOK-Pflichtmitgliedern ohne Rentner (Arbeitsunfähigkeitsfälle, Arbeitsunfähigkeitsfälle je 100.000 Pflichtmitglieder, Arbeitsunfähigkeitstage, Arbeitsunfähigkeitstage je 100.000 Pflichtmitglieder,Tage je Fall). Gliederungsmerkmale: Jahre, Deutschland, Geschlecht, ICD-10 (2008)

77. The EuroQol Group's International Task Force: Measuring Self-Reported Population Health: An International Perspective based on EQ-5D (2004)

78. Jit, M.: The risk of sequelae due to pneumococcal meningitis in high-income countries: A systematic review and meta-analysis. Journal of Infection 61(2), 114–124 (2010). doi: 10.1016/j.jinf.2010.04.008

79. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: Allgemeine Methoden. Version 4.2 vom 22.04.2015 (2015)

80. Moberley, S., Holden, J., Tatham, D.P., Andrews, R.M.: Vaccines for preventing pneumococcal infection in adults. The Cochrane database of systematic reviews(1), CD000422 (2013). doi: 10.1002/14651858.CD000422.pub3

81. Huss, A., Scott, P., Stuck, A.E., Trotter, C., Egger, M.: Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 180(1), 48–58 (2009). doi: 10.1503/cmaj.080734

Article 8

The role of decision-analytic modelling in German health technology assessments

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The Role of decision-analytic modelling in German health technology assessments

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Abstract

Background: Decision-analytic modelling (DAM) has become a widespread method in health technology assessments (HTA), but the extent to which modelling is used differs among international HTA institutions. In Germany, the use of DAM is optional within HTAs of the German Institute of Medical Documentation and Information (DIMDI). Our study examines the use of DAM in DIMDI HTA reports and its effect on the quality of information provided for health policies.

Methods: A review of all DIMDI HTA reports (from 1998 to September 2012) incorporating an economic assessment was performed. All included reports were divided into two groups: HTAs with DAM and HTAs without DAM. In both groups, reports were categorized according to the quality of information provided for healthcare decision making.

Results: Of the sample of 107 DIMDI HTA reports, 17 (15.9%) used DAM for economic assessment. In the group without DAM, conclusions were limited by the quality of economic information in 51.1% of the reports, whereas we did not find limited conclusions in the group with DAM. Furthermore, 24 reports without DAM (26.7%) stated that using DAM would likely improve the quality of information of the economic assessment.

Conclusion: The use of DAM techniques can improve the quality of HTAs in Germany. When, after a systematic review of existing literature within a HTA, it is clear that DAM is likely to positively affect the quality of the economic assessment DAM should be used.

Keywords: Health technology assessment; Health economic evaluation; Health economic modelling; Cost-effectiveness; Cost-utility; Decision analysis

Background

In the process of health technology assessment, decision-analytic modelling serves as an assessment approach for economic evaluation. Performing economic evaluation in the HTA has become a standard requirement of healthcare systems in many countries (e.g. the UK, Canada, Australia), and DAM has been accepted as a valid analytical approach. The method is applied to synthesize existing evidence on the costs and effectiveness of healthcare options and to determine an optimal strategy among them. In recent years, the use of DAM for HTA has significantly increased [1,2], and several studies providing good practice guidelines for the use of DAM in HTA have been conducted [2]. In particular, guidelines issued by HTA institutes in the UK and Canada provide detailed descriptions of the required elements of HTAs and the appropriate methods for decision modelling.

In Germany, HTA was introduced in the 1990s. In 1995, the German Federal Ministry of Health assembled a research group and assigned it to review, assess and prepare the implementation of data collection and to evaluate medical procedures and technologies in Germany [3]. HTA was formally approved in Germany with the healthcare reform in 2000. The German Agency for Health Technology Assessment (DAHTA) was established within the German Institute of Medical Documentation and Information (DIMDI). It was commissioned to implement and operate a database, an information system and a scientific working program on HTA [4,5]. The HTAs published by DIMDI aim to primarily inform health policy and not to provide recommendations for the benefits catalogue of the Statutory Health Insurance (SHI) [5]. These HTA reports include medical, economic, ethical, social and juridical aspects [6]. Following the SHI Modernization Act in 2004,

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HTA gained increasing importance in Germany. The Institute for Quality and Efficiency in Health Care (IQWiG) was established as an independent scientific body to perform technology assessments on behalf of the Federal Joint Committee (G-BA; a supreme decision making body of the self-governing healthcare system in Germany) or the Federal Ministry of Health. The technology assessments serve to inform the decision making by the G-BA [5], and the reports by IQWiG were limited to medical technology assessments. Since 2007, with the German Act on reinforcing SHI competition, IQWiG may also be commissioned to perform cost-benefit assessments.

The guidelines of both DIMDI and IQWiG indicate that DAM may be necessary for economic assessment of a technology [6,7]; however, the incorporation of a model is not a requirement for developing an HTA for publication by DIMDI, and DAM has become an optional tool in practice. IQWiG sees modelling as essential for economic assessment and requires it in the absence of comprehensive economic data [7]. Thus, IQWiG has released detailed information on the methods applied in modelling [8]. The DIMDI guidelines, which are summarized in its handbook, do not provide specific methodological recommendations for the development of DAM.

Considering the growing importance of performing systematic assessments of health technologies in Germany, it is desirable to continue working on the development of HTA methodologies, which may improve the quality of HTA reports. One important direction may be to enhance the application of decision models in German HTAs. Therefore, in our study, we review the use of DAM in German HTAs and analyse the effects of the use of DAM on the quality of information provided for healthcare decision making. We also study decision models applied to German settings and consolidate the main characteristics of the models developed by the German HTAs. Because IQWiG did not provide economic assessments by the time of our analysis, we based our work on the HTA reports published by DIMDI.

Methods

Search strategy and exclusion criteria

Using the DAHTA database, we identified and extracted all DIMDI HTA reports conducted during the period from 1998 to September 2012. HTAs that did not undertake economic assessments were excluded from the analysis. The resulting sample of HTAs was divided into two groups: HTAs that performed a systematic literature review and HTAs that developed a new decision-analytic model (designed for the characteristics of the German healthcare system) in addition to the literature review for the economic assessment.

Assessing the informativeness of HTA reports for decision making

In order to analyse the informativeness of HTAs for decision making, we developed an HTA classification based on the quality of information provided in each HTA report. We reviewed all included HTAs, focusing on the following sections: the summary, the conclusion and the answers provided to the research questions. Additionally, we checked for consistency between these sections. We defined three aggregate types that described the levels of informativeness of the HTA report.

'Conclusion': The HTA provides a clear conclusion regarding the medical effectiveness or cost-effectiveness of the health technology (technologies) under assessment. Uncertainty is low and further research is unlikely to affect the given conclusion.

'Limited conclusion': Authors on an HTA formulate a general suggestion regarding the medical effectiveness/cost-effectiveness of the health technology (technologies) under assessment, but the conclusion is limited because of the limitations of the reviewed evidence. Major limitations of the study are explained through either the low quality of the reviewed studies or the difficulties of applying the existing evidence to the German health care system. The latter generally occurs when conducting an economic assessment because of the differences in the healthcare structures and/or resource prices. In addition, the uncertainty is significant, and further research is likely to have a considerable effect on the results and may change the provided inferences.

'No conclusion': Authors of an HTA cannot provide an assessment of medical effectiveness and cost-effectiveness of the health technology (technologies) because of the lack of scientific evidence in the reviewed literature.

Assessing the impact of decision-analytic modelling on the informativeness of HTA reports

The medical effectiveness of interventions is a key input parameter in decision-analytic models. The evidence of medical effectiveness affects the quality of information provided in health economic evaluations. Low-quality medical evidence can be a barrier for conducting economic analysis. Consequently, the existing medical evidence has to be taken into account when assessing the impact of decision-analytic modelling on the informativeness of HTA reports. Therefore, we reviewed the medical part and the economic part of each HTA separately. Using the three types of informativeness, six categories (CAT I-VI) were formed to classify the HTA reports. Table 1 shortly sketches these categories. The first row and column of the table provide the level of information related to the medical and economic assessments, respectively. Combinations between the type of the medical part and the type the economic part constitute the six categories shown in the intersection cells of the table.

Table 1 Categorization of HTA conclusions based on the 'quality level' of information for decision making

		Economic assessment		
		Conclusion	Limited conclusion	No conclusion
Medical assessment	Conclusion	I	II	III
	Limited conclusion	not applicable	IV	V
	No conclusion	not applicable	not applicable	VI

In order to evaluate the impact of using DAM on the quality of information given in the economic portions of the HTAs, we compared medical and economic assessments of each report in the sample and analysed the difference between their levels of informativeness. HTA reports in CAT VI were excluded from the analysis, since the reports in this category provide insufficient medical evidence for progressing to economic evaluation. For each of the groups, 'HTA with a model' and 'HTA without a model', we determined the percentage of HTAs in which the economic assessment provides significantly lower quality of information than the medical assessment (CATs II, III and V). We compared "with-" and "without a model" groups based on these percentages to reduce potential bias, in case both groups are not comparable with respect to the reported level of information in the medical assessment.

The review and the classification of the reports were undertaken by two researchers independently, and any distinctions were discussed and clarified. The HTA reports with new model development were further analysed with respect to the applied modelling methods. The aim of the further analyses was to characterize and compare the techniques used that focused on the selected key components of modelling: the economic evaluation type, the model type, the time horizon, the perspective, the primary medical outcome, the discount factor and the type of sensitivity analyses. These components were extracted according to the individual descriptions provided in the HTA reports.

Results

Sample size

In the period from 1998 to September 2012, 158 DIMDI–HTA reports were conducted, published and indexed in the DAHTA database. Of these, 20 methodological reports were excluded during the screening process. Another 31 reports did not meet the inclusion criterion of an economic assessment of the health technology. The resulting sample of 107 HTA reports was divided into reports that include the development of a new model for the German healthcare system and those that only performed a systematic literature review for economic assessment. In total, 17 HTA reports (approximately 16%) developed such a model, whereas the other 90 reports did not. Figure 1 summarizes the selection procedure (A list of all identified reports is presented in the Additional file 1: Table S2 to Table S5).

Informativeness of DAHTA reports

The medical and economic parts of the 107 HTAs in our sample are grouped into the three aggregate types. Of our sample, 29 reports (27.1%) state a clear conclusion regarding the medical effectiveness of a technology in the assessment, and 15 reports (14%) provide a conclusion regarding cost-effectiveness in the economic section. Another 44 reports (41.1%) state a general suggestion on medical effectiveness. The conclusion on cost-effectiveness is significantly limited in 36 reports (33.6%). In 34 reports (31.8%), it is not possible to conduct a medical assessment because of the lack of scientific evidence in the reviewed literature. An economic conclusion could not be drawn in 56 reports (52.3%), either because of the lack of economic evidence or because the results of the international studies are not applicable to the German setting. Figure 2 shows the results of the division of the reports into the types for the groups of 'HTAs with a model' and 'HTAs without a model'. In the sample of HTAs with a model, a higher percentage of reports provide information for decision making in the medical assessment compared to the sample of HTAs without a model (conclusion is given in 52.9% vs. 22.2%; conclusion is limited in 41.2% vs. 41.1%). Of the reports that applied DAM, 94.1% provide either a clear conclusion (32.2%) or a limited conclusion (61.1%) on the cost-effectiveness of the technology/technologies under assessment compared with 38.9% in the group without a model (conclusion: 6.7%; limited conclusion: 32.2%).

Overall, the proportion of HTA reports that provide information on the assessed health technology for decision making (CAT I–V) is 68.2% (73 out of 107 reports), of which 15 reports draw a clear conclusion on both the medical and economic assessments (CAT I). Another 14 reports either draw a clear conclusion on effectiveness but provide only a general suggestion on cost-effectiveness (CAT II; seven reports), or they are not able to provide a conclusion on cost-effectiveness based on the reviewed evidence (CAT III; seven reports). Of the 44 reports that provide a general suggestion on medical effectiveness, 29 reports also provide a general suggestion on cost-effectiveness (CAT IV) and 15 are not able to assess the cost-effectiveness because of a lack of evidence (CAT V). In addition, 31.8% (34 of 107 reports) of the reports are grouped in CAT VI, because they cannot draw a conclusion on medical effectiveness or cost-effectiveness.

Among the 90 HTAs without a new model 57 (63.3%) give information for decision making (CAT I–V). The majority of these (51 reports) provide only a general opinion on the medical effectiveness or cost-effectiveness of the health technology (technologies) under assessment (CAT II–V); thus, further research is likely to have an important effect and may

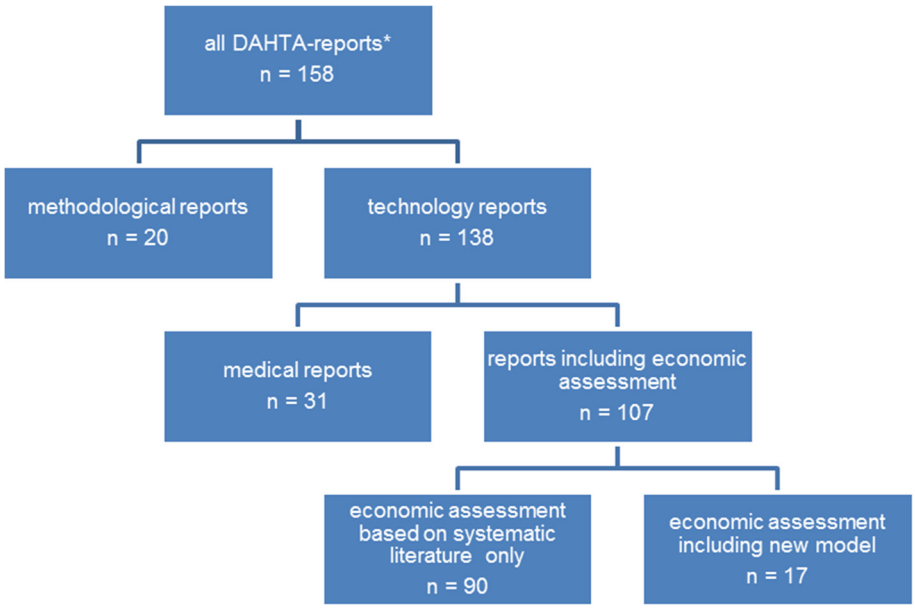

Figure 1 Selection process for report inclusion. *As of September 2012.

change the conclusion. The number of the reports in CATs II, III, IV and V are 7, 7, 22 and 15, respectively.

The HTA reports with a developed model provide information for decision making (CAT I–V) in 16 out of the 17 cases (94.1%). Of these, nine HTAs draw a clear conclusion and provide high-quality information in both the medical and economic assessment (CAT I), and seven HTAs provide a general suggestion on both effectiveness and cost-effectiveness (CAT IV).

Impact of decision-analytic modelling on informativeness of DAHTA reports

Of the HTA reports that did not develop a decision-analytic model for the German healthcare system, 51.1% provide significantly less information in the economic assessment compared with the medical assessment. Of the 20 reports that provide a conclusion in the medical assessment, 7 provide suggestions in the economic assessment and another 7 cannot draw a conclusion. Of the 37 reports with a limited conclusion on effectiveness in the medical assessment, 15 reports provide no information on cost-effectiveness in the economic assessment. In the group of HTAs that apply DAM techniques, no report provides significantly less information in the economic assessment compared with the medical assessment. Figure 3 illustrates the results for both groups.

Additionally, we reviewed the proportion of HTAs that reported a requirement for further economic research. The majority of these reports (86 of 107) conclude that additional economic evidence is required in the literature. Of the 90 reports that conduct only an economic systematic literature research, 26.7% (24 reports) state that the development of a model is likely to improve the quality of information of the economic assessment. Six of the HTAs that used DAM provide recommendations to update the models as soon as new medical evidence is available.

Economic evaluations for the German settings are retrieved in 36 of 107 HTA reports; however, none of these evaluations significantly affected the level of information in the economic assessments, mainly because of either the low quality of the evaluation or the use of outdated economic or medical data.

Characteristics of decision-analytic models

Seventeen of the HTA reports in our sample developed new decision-analytic models for the German settings. Here, we provide a review of these and focus on the selected key components of health economic modelling. Table 1 in the supplements summarizes the results. One model was not completed because of the lack of medical evidence of important input parameters, and this model is excluded from the following review.

Type of economic evaluation

Overall, 10 cost-effectiveness analyses and 2 cost-utility analyses were conducted within the 16 HTAs. Three HTA reports include examination of costs, and one report includes both a cost-effectiveness analysis and a cost-utility analysis.

Model type

The applied DAM techniques are identified in 63% (10 of 16) of the HTAs. In six HTAs, economic evaluations are based on Markov models. Three HTA reports apply

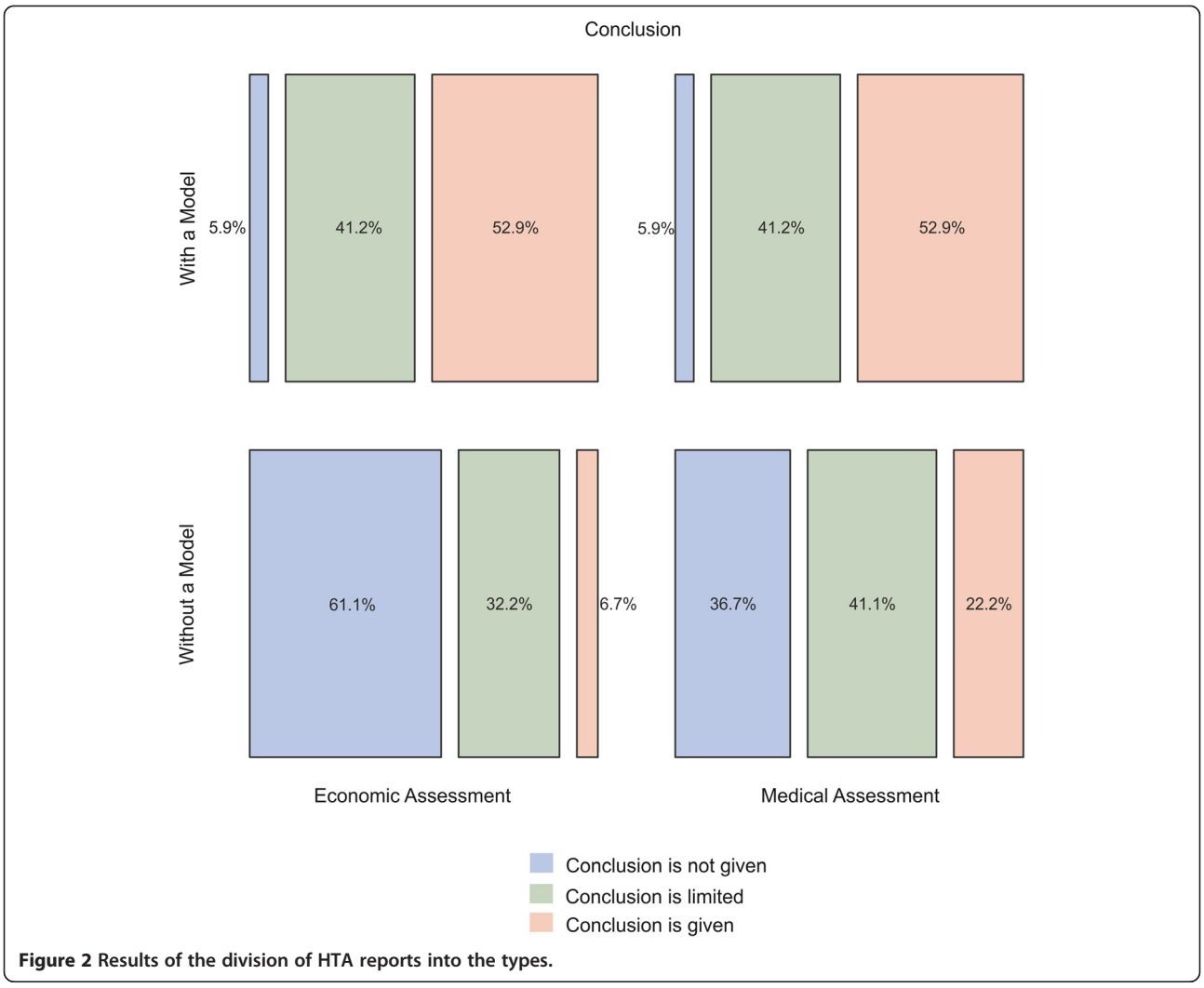

Figure 2 Results of the division of HTA reports into the types.

decision trees. One report uses combinations of a decision tree and the Markov model. Another report presents a Markov chain Monte Carlo simulation in which, in contrast with common cohort modelling, virtual patients are simulated on an individual level with the implication of a stochastic process (i.e. a micro-simulation). The remaining six HTAs calculate results on the basis of simple calculations.

Discount factor

Overall, 11 of the 16 models apply a discount rate in the economic evaluations. Of these, six models use a 3% annual discount rate and five models use a 5% discount rate for both health effects and costs. In one model, it is unnecessary to discount because the economic evaluation is performed for a short time horizon (1 year). One model omits discounting of the costs and benefits, albeit it performs the economic evaluation for a time horizon of 3 years. The other three models report no discount rate.

Perspective

Of the 16 reviewed models, four state a social perspective. Three models describe the perspective as a narrowed social perspective. The perspective of two models is that of the German statutory health insurance. One model uses the scope of a healthcare provider and includes additional costs in its evaluation. Five models state no perspective; however, the outcomes of the models probably reflect the perspective of the statutory health insurance. One model uses the perspective of the German healthcare system.

Primary medical outcome

Three models use life years to value health outcomes and two models use QALYs. One model bases the economic evaluation on both life years and QALYs. The rest of the models calculate health outcomes specific to the character of the disease or the technology under assessment.

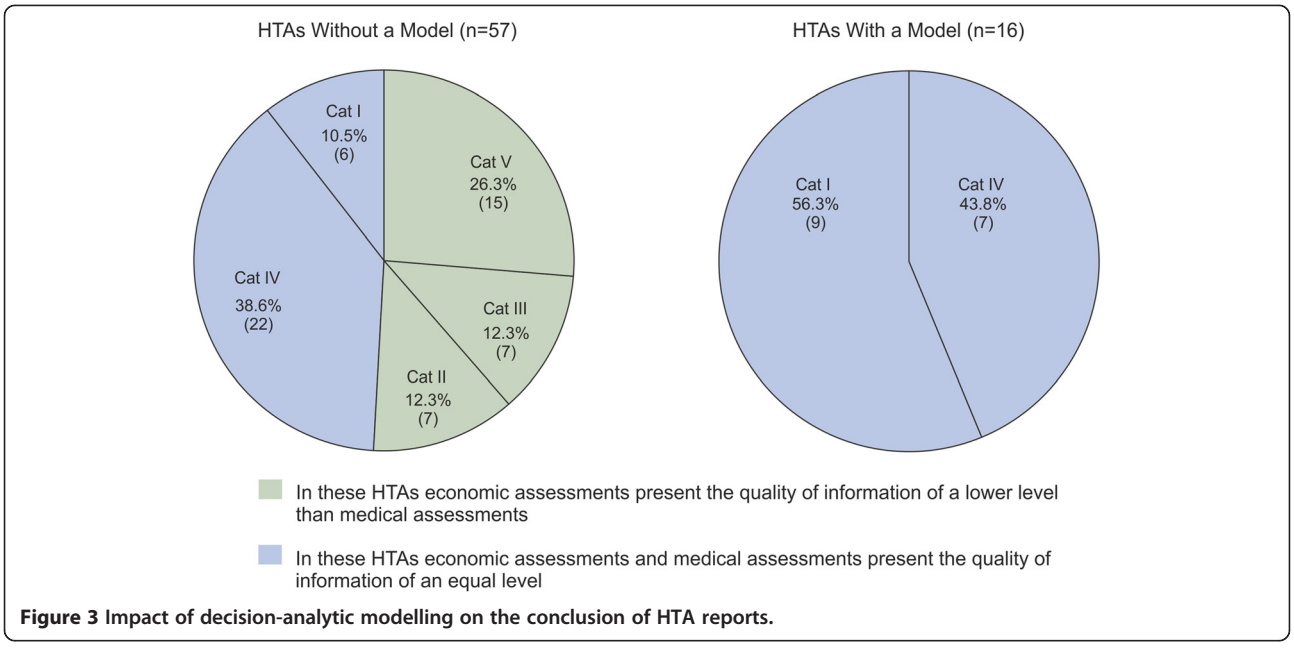

Figure 3 Impact of decision-analytic modelling on the conclusion of HTA reports.

Type of sensitivity analysis

All 16 models conduct sensitivity analyses. All models apply a one-way sensitivity analysis; in addition, three reports also perform a multi-way analysis and two perform a probabilistic sensitivity analysis.

Discussion

Following the objective of this work, we searched for evidence that developing a new decision-analytical model improves the quality of information of HTAs for decision making in the German healthcare sector.

Therefore, we reviewed all HTAs published from DIMDI that included economic assessments and classified them according to the quality level of the information provided for decision making. The results of this study suggest that HTAs perform better when they build a new decision model for economic evaluation. Particularly, the review showed that all HTAs with developed models were capable of providing economic evidence for decision making with the quality of the information at least equivalent to that provided by the medical portion. In contrast, over 50% of HTA reports without model gave a lower level of information in the economic assessments than in the medical assessment. Moreover, approximately 80% of the reviewed HTAs concluded that there is a need for further economic research, and 27% (24 reports) of the HTAs without a model stated that the development of a decision-analytic model might improve the quality of the information of the economic assessment. These findings indicate that using DAM in DAHTA reports is not related to the need for additional economic information.

In our analysis, we also found differences between the models in their quality and complexity. The review of HTAs with models indicated that cost-effectiveness analysis with Markov models was the preferred type of economic evaluation. Although the majority of the selected HTAs with models incorporated the key elements of modelling, some differences in the applied methods were observed. These differences occurred in valuing medical outcomes, the stated perspectives and the applied annual discount rate. Not all the applied methods were up-to-date. For example, for addressing uncertainty, a one-way sensitivity analysis but no probabilistic sensitivity analysis was mostly conducted.

Current shortcomings of the HTA reports and the differences between the applied methods might complicate decision making processes and might decrease the role of HTAs as sources of information in healthcare. Elaboration of official standards and recommendations on the use of decision-analytic models in HTA might solve the discrepancies in the applied methods. Imposing a requirement of justifying and clarifying the necessity for modelling seems to be useful. Thus, requiring DAM is necessary when, after conducting a systematic literature review, it is justified that a model would improve the results of assessment in terms of informing decision making.

The current description of the HTA methods by DIMDI lacks guidance on both, methods for conducting decision modelling and for assessment of cost-effectiveness (e.g. ICER vs. the Efficiency Frontier of the IQWiG [7]). Since these aspects are interconnected, they are both essential for the production of consistent results among HTAs. For instance, if the assessment of cost-effectiveness

allows for comparisons between health outcomes, a generic measure such as QALY should be applied in modelling. When developing a guide on decision modelling in HTA, both the modelling methods and the assessment of outcomes must be considered. Additionally, it is desirable to consider the requirements and needs of the users of HTA reports. For instance, requests by decision makers may determine the applied perspective (e.g. societal or sickness funds).

Some limitations of this study should be considered when contemplating the results. First, because of the diversity and complexity of the HTAs conclusions provided, the types and categories of our classifications are broadly defined. A more precise grouping might change the results of the classifications, but it would unlikely affect the overall conclusion of our study. Second, the classifications were performed based on the concluding statements provided by the authors of the HTAs; therefore, we did not conduct an assessment of the evidence reviewed in the reports. Among the HTA researchers, distinctions in valuing the existing evidence may exist. These differences might in turn bias our work.

Despite the limitations, this study provides new information on conducting HTA in Germany regarding the use of DAM. It also indicates the lack of economic research in the German HTAs as well as the need for increased and improved economic evaluations conducted for HTAs.

Conclusion

Our review shows that it is necessary to improve economic evaluations for HTAs produced in Germany. The results of the analysis suggest that the use of modelling improves the quality of economic assessment and thereby the overall performance of an HTA, however, the number of HTAs that conduct modelling is small. In order to enhance the quality of HTAs in Germany, it is desirable to develop a procedure for incorporating decision-analytic models in the economic assessments of reports. As long as the application of modelling is not necessary for every HTA study, it seems reasonable to develop a model on request after a systematic literature review clarifies that DAM is likely to have a positive impact on the economic assessment quality. In order to guarantee good modelling quality and consistency of the applied methods, designing and expanding the good practices guide for the use of DAM for DIMDI–HTAs is required.

Additional file

Additional file 1: Technology reports with economic assessment based on systematic literature review.

Competing interests
Sebastian Braun is the national winner of the 2010/2011 HTAcademy scholarship, which was sponsored by Pfizer Deutschland GmbH.

Authors' contributions
AK contributed to the study design, review of Health Technology Assessments, data analysis and interpretation and drafted the manuscript. MT contributed to the review of Health Technology Assessments, data analysis and interpretation and drafted the manuscript. SB contributed to the study design, interpretation of the results and drafted the manuscript. JMGvdS contributed to the study design and revised the manuscript for important intellectual content.All authors read and approved the final manuscript.

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References

1. Draborg E, Gyrd-Hansen D. Time-trends in health technology assessments: an analysis of developments in composition of international health technology assessments from 1989 to 2002. Int J Technol Assess Health Care. 2005;21:492–8.
2. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics. 2006;24:355–71.
3. Greiner W, 'Bestandsaufnahme, Bewertung und Vorbereitung der Implementierung einer Datensammlung, Evaluation medizinischer Verfahren und Technologien in der Bundesrepublik'. Health Technology Assessment (HTA). In: Schöffski O, von der Graf Schulenburg J-M, editors. Gesundheitsökonomische Evaluationen. 3rd ed. Berlin, Heidelberg: Springer-erlag; 2012. p. 457–79.
4. Perleth M, Gibis B, Gohlen B. A short history of health technology assessment in Germany. Int J Technol Assess Health Care. 2009;25(1):112–9.
5. Fricke F, Dauben HP. Health technology assessment: a perspective from Germany. Value Health. 2009;12(2):S20–7.
6. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI): Handbuch für Autoren zur Erstellung von HTA-Berichten. Version: 02_08. [http://www.dimdi.de/static/en/hta/dahta/prozess/handbuch.pdf]
7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): General Methods for evaluating the relation between cost and benefit - version 1.0. [https://www.iqwig.de/download/General_Methods_for_the_Assessment_of_the_Relation_of_Benefits_to_Costs.pdf]
8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): Working Paper on Modelling in health economic evaluations. [https://www.iqwig.de/download/Working_Paper_Modelling.pdf]

Supplementary Material

Table S1: Summary of basic modelling methods in Health Technology Assessments of the German Institute of Medical Documentation and Information (DIMDI)

Author	Year	Indication	Intervention type	Type of economic evaluation	Model type	Time horizon	Perspective	Primary clinical outcome	Discount factor	Type of sensitivity analyses
Aidelsburger et al.*	2003	Osteoporosis	Screening	Cost-effectiveness	Hybrid (decision tree + markov model)	Life time	ns	ns	ns	ns
Siebert et al.	2003	Cervical carcinoma	Screening	Cost-effectiveness	Markov model	Life time	Social	Life years	3%	One-way, two-way
Siebert et al.	2003	Hepatitis C	Treatment	Cost-effectiveness, cost-utility	Markov model	Life time	Social	Life years, QALY	3%	One-way, multi-way
Corzillius et al.	2003	HIV	Diagnostics	Cost-effectiveness	Markov model	Life time	Health care system	Life years	5%	One-way, multi-way, probabilistic
Dauben et al.	2004	Hearing disorder	Screening	Cost-effectiveness	Markov model	10 (16) years	ns	time with correct diagnosis	3%	One-way
Frank et al.	2004	Cervical carcinoma	Screening	Cost-effectiveness	Decision tree	40 years	ns	Correct diagnosed cases	ns	One-way
Gorenoi et al.	2005	Coronary heart disease	Treatment	Cost-effectiveness	ns	1 year, life time	ns	Avoided revasculations	ns	One-way
Zahn et al.	2006	Obstretrics	Treatment	Cost-analysis	Decision tree	2 weeks, 50 years	Care provider + additional costs	Not relevant	3%	One-way
Schnell-Inderst et al.	2006	Hearing Disorder	Screening	Cost-effectiveness	Markov Model	10 years	ns	Time with correct diagnosis	3%	One-way
Gorenoi et al.	2006	Appendicitits	Treatment	Cost-analysis	ns	ns	ns	Not relevant	ns	One-way
Siebert et al.	2008	Coronary heart disease	Treatment	Cost-utility	Hybrid (decision tree + markov model)	Life time	Social	QALY	5%	One-way
Gorenoi et al.	2008	Peripheral arterial disease	Treatment	Cost-effectiveness	ns	1 year	Narrowed social	Prevented restenosis, revascularization	Not relevant	One-way
Gorenoi et al.	2008	Coronary heart disease	Treatment	Cost-analysis	ns	1 year, 3 years	Narrowed social	Number of deaths, heart attacks**	None	One way
Schmieder et al.	2010	Brain tumor (meningioma)	Treatment	Cost-utility	Markov chain monte carlo simulation	Life time	Statutory health insurance	QALY	5%	One-way, probabilistic
Sroczynski et al.	2010	Cervical carcinoma / HPV	Screening	Cost-effectiveness	Markov model	Life time	Statutory health insurance	Life years	3%	One-way, multi-way
Gorenoi et al.	2011	Stable angina pectoris	Treatment	Cost-effectiveness	ns	5 years	Narrowed social	Prevented angina pectoris episodes	5%***	One-way
Gorenoi et al.	2012	Coronary heart disease	Diagnostics	Cost-effectiveness	ns	10 years	Social	Correct diagnosis	5%	One-way

* Due to a lack of medical evidence, only the structure of the model was reported.
** Cost-effectiveness not calculated.
*** Only in sensitivity analysis.

Table S2: Technology reports with economic assessment based on systematic literature review (n=90); included

Document Number	Authors	Year	Titel
DAHTA023	Perleth M; Kochs G	1999	Stenting versus Ballondilatation bei koronarer Herzkrankheit. Systematische Übersichten zur medizinischen Effektivität und zur Kosten-Effektivität
DAHTA016	Bitzer EM; Greiner W	2000	Hochdosis-Chemotherapie mit autologer Stammzelltransplantation zur Therapie des metastasierenden Mammakarzinoms
DAHTA019	Siebert U; Mühlberger N; Behrend C; Wasem J	2001	PSA-Screening beim Prostatakarzinom - systematischer gesundheitsökonomischer Review
DAHTA020	Müller A; Stratmann-Schöne D; Klose T; Leidl R	2001	Ökonomische Evaluationen der Positronen-Emissions-Tomographie
DAHTA021	Perleth M; Leyen U von der; Schmitt H; Dintsios CM; Felder S; Schwartz FW; Teske S	2003	Das Schlaf-Apnoe-Syndrom - systematische Übersichten zur Diagnostik, Therapie und Kosten-Effektivität
DAHTA028	Kulp W; Garrido Velasco M; Greiner W; Schulenburg JM Graf von der	2003	Die Verwendung des Excimer Lasers in der refraktiven Augenchirurgie
DAHTA032	Kulp W; Greiner W; Schulenburg JM Graf von der	2003	Bewertung der Möglichkeiten und Verfahren zur Aufbereitung medizinischer Einwegprodukte
DAHTA033	Olbrich A; Felder S	2003	Knochen- und Knochenersatzmaterialien zur parodontalen Regeneration oder zum Knochenaufbau für Implantate
DAHTA064	Felder S; Meyer FP	2003	Glycoprotein IIb/IIIa-Rezeptorantagonisten in der Therapie akuter koronarer Syndrome - ein gesundheitsökonomischer HTA-Bericht
DAHTA066	Siebert U; Aidelsburger P; Peeters J; Regar E; Mühlberger N; Klauss V; Rieber J; Corzillius M; Wasem J	2003	Wertigkeit des Einsatzes der intravaskulären Ultraschallbildgebung (IVUS) im Rahmen von diagnostischen und therapeutischen Herzkatheteruntersuchungen - ein gesundheitsökonomischer HTA-Bericht
DAHTA076	Gerhardus A; Jalilvand N; Heintze C; Krauth C	2003	Ein Vergleich verschiedener chirurgischer Verfahren zur elektiven Leistenhernienoperation bei Erwachsenen - ein Health Technology Assessment
DAHTA077	Gorenoi V; Siebert U; Perleth M; Brundobler M; Dintsios CM; Klauss V; Rieber J; Wasem J; Leidl R	2003	Stenting versus Ballondilatation bei koronarer Herzkrankheit
DAHTA075	Kulp W; Corzillius M; Greiner W; Pientka L; Siebert U; Schulenburg JM Graf von der; Wasem J	2005	Wertigkeit von Tumor-Nekrose-Faktor-alpha-Antagonisten in der Behandlung der Rheumatoiden Arthritis
DAHTA084	Vauth C; Englert H; Fischer T; Kulp W; Greiner W; Willich SN; Stroever B; Schulenburg JM Graf von der	2005	Sonographische Diagnostik beim akuten Abdomen bei Kindern und Erwachsenen
DAHTA108	Lühmann D; Burkhardt-Hammer T; Borowski C; Raspe H	2005	Minimal-invasive Verfahren zur Behandlung des Bandscheibenvorfalls
DAHTA109	Habl C; Bodenwinkler A; Stürzlinger H	2005	Wurzelbehandlung an Molaren
DAHTA111	Gorenoi V; Kulp W; Greiner W; Schulenburg JM Graf von der	2005	Thrombozytenaggregationshemmer zur Primär- und Sekundärprävention des ischämischen Schlaganfalls
DAHTA114	Antony K; Pichlbauer E; Stürzlinger H	2005	Medizinische und ökonomische Effektivität der Pneumokokkenimpfung für Säuglinge und Kleinkinder
DAHTA115	Frank W; Konta B	2005	Bluthochdruckleitlinien und ihre Auswirkungen auf das Gesundheitssystem
DAHTA116	Braun S; Behrens T; Kulp W; Eberle A; Greiner W; Ahrens W; Schulenburg JM Graf von der	2005	Neuraminidasehemmer in der Therapie und Postexpositionsprohylaxe der Influenza
DAHTA119	Hessel F; Grabein K; Schnell-Inderst P; Siebert U; Caspary W; Wasem J	2005	Extrakorporale artifizielle Leberunterstützungssysteme bei akutem Leberversagen oder einer akuten Dekompensation eines chronischen Leberleidens
DAHTA123	Frank W; Konta B	2005	Kognitives Training bei Demenzen und andere Störungen mit kognitiven Defiziten
DAHTA128	Eberhardt S; Heinemann A; Kulp W; Greiner W; Leffmann C; Leutenegger M; Anders J; Pröfener F; Balmaceda U; Cordes O; Zimmermann U; Schulenburg JM Graf von der	2005	Dekubitusprophylaxe und -therapie
DAHTA130	Carvalho Gomes H de; Velasco-Garrido M; Busse R	2005	Screening auf urogenitale Chlamydia trachomatis-Infektionen
DAHTA118	Frank W; Konta B; Seiler G	2006	Therapie des unspezifischen Tinnitus ohne Ursache
DAHTA120	Eidt D; Roll S; Kulp W; Müller-Nordhorn J; Vauth C; Greiner W; Willich SN; Schulenburg JM Graf von der	2006	Bypassmaterialien in der Gefäßchirugie
DAHTA121	Aidelsburger P; Grabein K; Huber A; Hertlein H; Wasem J	2006	Die elastisch stabile intramedulläre Nagelung bei instabilen kindlichen Unterarmschaftfrakturen
DAHTA124	Stürzlinger H; Antony K; Pichlbauer E	2006	Koronarkalkbestimmung mit CT-Verfahren bei asymptomatischen Risikopatienten
DAHTA125	Heinen-Kammerer T; Wiosna W;	2006	Monitoring von Herzfunktionen mit Telemetrie

	Nelles S; Rychlik R		
DAHTA129	Claes C; Kulp W; Greiner W; Schulenburg JM Graf von der; Werfel T	2006	Therapie der mittelschweren und der schweren Psoriasis
DAHTA132	Frank W; Konta B; Prusa N; Raymann C	2006	Bedeutung der intensivierten Pflege
DAHTA133	Rosian I; Pichlbauer E; Stürzlinger H	2006	Einsatz von Statinen in der Primärprävention
DAHTA134	Lühmann D; Burkhardt-Hammer T; Stoll S; Raspe H	2006	Prävention rezidivierender Rückenschmerzen- Präventionsmaßnahmen in der Arbeitsplatzumgebung
DAHTA135	Schnell-Inderst P; Kossmann B; Fischereder M; Klauss V; Wasem J	2006	Antioxidative Vitamine zur Prävention kardiovaskulärer Erkrankungen nach Nierentransplantation und bei chronischer Niereninsuffizienz
DAHTA136	Walter U; Krauth C; Wienold M; Dreier M; Bantel S; Droste S	2006	Verfahren zur Steigerung der Teilnahmerate an Krankheitsfrüherkennungsprogrammen
DAHTA140	Rohde V; Grabein K; Hessel F; Siebert U; Wasem J	2006	Orchiektomie versus medikamentöse Therapie mit LH-RH-Analoga zur Behandlung des fortgeschrittenen Prostatakarzinoms
DAHTA141	Frank W; Konta B	2006	Bypassoperation am schlagenden Herzen im Vergleich zur Operation mit Unterstützung durch die Herz-Lungen-Maschine
DAHTA142	Werfel T; Claes C; Kulp W; Greiner W; Schulenburg JM Graf von der	2006	Therapie der Neurodermitis
DAHTA145	Bockelbrink A; Rasch A; Roll S; Willich SN; Greiner W	2006	Welche Auswirkung hat die Kataraktoperation auf das Entstehen oder das Fortschreiten einer altersbedingten Makuladegeneration (AMD)?
DAHTA127	Eberhardt S; Keil T; Kulp W; Greiner W; Willich SN; Schulenburg JM Graf von der	2007	Hormone zur Therapie von Beschwerden im Klimakterium und zur Primärprävention von Erkrankungen in der Postmenopause
DAHTA138	Rosian-Schikuta I; Fröschl B; Habl C; Stürzlinger H	2007	Die Masern-Mumps-Röteln-Impfung aus gesundheitspolitischer und ökonomischer Sicht
DAHTA144	Antony K; Genser D; Fröschl B	2007	Erkennungsgüte und Kosteneffektivität von Screeningverfahren zur Erfassung von primären Offenwinkelglaukomen
DAHTA146	Busch M; Haas S; Weigl M; Wirl C; Horvath I; Stürzlinger H	2007	Langzeitsubstitutionsbehandlung Opioidabhängiger
DAHTA147	Schumacher H; Müller-Nordhorn J; Roll S; Willich SN; Greiner W	2007	Drotrecogin alfa (aktiviert) bei der Behandlung der schweren Sepsis
DAHTA149	Stürzlinger H; Fröschl B; Genser D	2007	Wertigkeit der optischen Kohärenztomographie im Vergleich zur Fluoreszenzangiographie in der Diagnostik der altersbedingten Makuladegeneration (AMD)
DAHTA187	Gorenoi V; Schönermark MP; Hagen A	2007	Nutzen und Risiken hormonaler Kontrazeptiva bei Frauen
DAHTA189	Angermayr L; Velasco Garrido M; Busse R	2007	Künstliche Ventrikel bei fortgeschrittener Herzinsuffizienz
DAHTA195	Lühmann D; Schramm S; Raspe H	2007	Wie ist der derzeitige Stellenwert der Homozysteinbestimmung im Blut als Risikofaktor für die koronare Herzkrankheit (KHK)?
DAHTA198	Nocon M; Mittendorf T; Roll S; Greiner W; Willich SN; Schulenburg JM Graf von der	2007	Welchen medizinischen und gesundheitsökonomischen Nutzen hat die Kolposkopie als primäres Screening auf das Zervixkarzinom?
DAHTA199	Mittendorf T; Nocon M; Roll S; Mühlberger N; Sroczynski G; Siebert U; Willich SN; Schulenburg JM Graf von der	2007	HPV-DNA-Diagnostik zur Zervixkarzinomfrüherkennung
DAHTA206	Gorenoi V; Schönermark MP; Hagen A	2007	Maßnahmen zur Verbesserung der Compliance bzw. Adherence in der Arzneimitteltherapie mit Hinblick auf den Therapieerfolg
DAHTA143	Friedrich M; Müller-Riemenschneider F; Roll S; Kulp W; Vauth C; Greiner W; Willich SN; Schulenburg JM Graf von der	2008	Vergleich der laparoskopischen Narbenhernioplastik und der konventionellen Operation mit und ohne Netzeinlage – Effektivität und Kostennutzenrelation
DAHTA186	Fröschl B; Arts D; Leopold C	2008	Topische antientzündliche Behandlung der Neurodermitis im Kindesalter
DAHTA203	Bockelbrink A; Stöber Y; Roll S; Vauth C; Willich SN; Greiner W	2008	Medizinische und ökonomische Beurteilung der bariatrischen Chirurgie (Adipositaschirurgie) gegenüber konservativen Strategien bei erwachsenen Patienten mit morbider Adipositas
DAHTA204	Konta B; Frank W	2008	Die Therapie der Parkinsonerkrankung mit Dopaminagonisten
DAHTA205	Frank W; Pfaller K; Konta B	2008	Mundgesundheit nach kieferorthopädischer Behandlung mit festsitzenden Apparaten
DAHTA213	Clar C; Velasco-Garrido M; Gericke C	2008	Interferone und Natalizumab in der Behandlung der multiplen Sklerose (MS)
DAHTA224	Antony K; Hiebinger C; Genser D; Windisch F	2008	Haltbarkeit von Zahnamalgam im Vergleich zu Kompositkunststoffen
DAHTA232	Müller-Riemenschneider F; Rasch A; Bockelbrink A; Vauth C; Willich SN; Greiner W	2008	Wirksamkeit und Wirtschaftlichkeit von verhaltensbezogenen Maßnahmen zur Prävention des Zigarettenrauchens
DAHTA215	Rieckmann N; Schwarzbach C; Nocon M; Roll S; Vauth C; Willich SN; Greiner W	2009	Pflegerische Versorgungskonzepte für Personen mit Demenzerkrankungen
DAHTA216	Schnell-Inderst P; Schwarzer R; Göhler A; Grandi N; Grabein K; Stollenwerk B; Klauss V; Wasem J;	2009	Stellenwert des hochsensitiven C-reaktiven Proteins (hs-CRP) als Marker für Herzinfarktgefährdung

	Siebert U		
DAHTA217	Stürzlinger H; Genser D; Hiebinger C; Windisch F	2009	ffektivität und Effizienz der CT-Koloskopie im Vergleich zur konventionellen Koloskopie in der Dickdarmkrebsdiagnose und -früherkennung
DAHTA225	Müller-Riemenschneider F; Schwarzbach C; Bockelbrink A; Ernst I; Vauth C; Willich SN; Schulenburg JM Graf von der	2009	Medizinische und gesundheitsökonomische Bewertung der Radiochirurgie zur Behandlung von Hirnmetastasen
DAHTA228	Stürzlinger H; Hiebinger C; Pertl D; Traurig P	2009	Computerized Physician Order Entry – Wirksamkeit und Effizienz elektronischer Arzneimittelverordnung mit Entscheidungsunterstützungssystemen
DAHTA234	Damm O; Nocon M; Roll S; Vauth C; Willich SN; Greiner W	2009	Impfung gegen humane Papillomaviren (HPV) zur Prävention HPV 16/18 induzierter Zervixkarzinome und derer Vorstufen
DAHTA236	Brunner-Ziegler S; Fröschl B; Hiebinger C; Wimmer A; Zsifkovits J	2009	Effektivität und Kosteneffizienz von Phosphatbindern in der Dialyse
DAHTA242	Fröschl B; Haas S; Wirl C	2009	Prävention von Adipositas bei Kindern und Jugendlichen (Verhalten- und Verhältnisprävention)
DAHTA248	Weinmann S; Schwarzbach C; Begemann M; Roll S; Vauth C; Willich SN; Greiner W	2009	Verhaltens- und fertigkeitenbasierte Frühinterventionen bei Kindern mit Autismus
DAHTA257	Nocon M; Kuhlmann A; Leodolter A; Roll S; Vauth C; Willich SN; Greiner W	2009	Medizinischer und gesundheitsökonomischer Nutzen der Untersuchung auf Helicobacter pylori-Besiedlung mittels 13C-Harnstoff-Atemtest in der Primärdiagnostik im Vergleich zu invasiven und nichtinvasiven diagnostischen Verfahren
DAHTA261	Müller-Riemenschneider F; Damm K; Meinhard C; Bockelbrink A; Vauth C; Willich SN; Greiner W	2009	Nichtmedikamentöse Sekundärprävention der koronaren Herzkrankheit (KHK)
DAHTA254	Hagen A; Gorenoi V; Schönermark MP	2010	Spezifische Immuntherapie (SIT) zur Behandlung der allergischen Rhinitis
DAHTA256	Tinnemann P; Stöber Y; Roll S; Vauth C; Willich SN; Greiner W	2010	Zahnmedizinische Indikationen für standardisierte Verfahren der instrumentellen Funktionsanalyse unter Berücksichtigung gesundheitsökonomischer Gesichtspunkte
DAHTA258	Grimm C; Köberlein J; Wiosna W; Kresimon J; Kiencke P; Rychlik R	2010	Diabetesneuentstehung unter antihypertensiver Therapie
DAHTA262	Buchberger B; Follmann M; Freyer D; Huppertz H; Ehm A; Wasem J	2010	Bedeutung von Wachstumsfaktoren für die Behandlung von chronischen Wunden am Beispiel des diabetischen Fußulcus
DAHTA263	Korczak D; Schöffmann C	2010	Medizinische Wirksamkeit und Kosten-Effektivität von Präventions- und Kontrollmaßnahmen gegen Methicillin-resistente Staphylococcus aureus (MRSA)-Infektionen im Krankenhaus
DAHTA267	Benkert D; Krause KH; Wasem J; Aidelsburger P	2010	Medikamentöse Behandlung der ADHS (Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung) im Erwachsenenalter in Deutschland
DAHTA268	Geiseler J; Karg O; Börger S; Becker K; Zimolong A	2010	Invasive Heimbeatmung insbesondere bei neuromuskulären Erkrankungen
DAHTA278	Korczak D; Kister C; Huber B	2010	Differentialdiagnostik des Burnout-Syndroms
DAHTA279	Korczak D; Huber B; Steinhauser G; Dietl M	2010	Versorgungssituation und Wirksamkeit der ambulanten im Vergleich mit der stationären pneumologischen Rehabilitation
DAHTA280	Schnell-Inderst P; Hunger T; Hintringer K; Schwarzer R; Seifert-Klauss V; Gothe H; Wasem J; Siebert U	2011	Individuelle Gesundheitsleistungen
DAHTA299	Buchberger B; Heymann R; Huppertz H; Friepörtner K; Pomorin N; Wasem J	2011	Effektivität von Maßnahmen der betrieblichen Gesundheitsförderung (BGF) zum Erhalt der Arbeitsfähigkeit von Pflegepersonal
DAHTA300	Korczak D; Steinhauser G; Dietl M	2011	Effektivität von Maßnahmen im Rahmen primärer Prävention am Beispiel kardiovaskulärer Erkrankungen und des metabolischen Syndroms
DAHTA301	Dietl M; Korczak D	2011	Versorgungssituation in der Schmerztherapie in Deutschland im internationalen Vergleich hinsichtlich Über-, Unter- oder Fehlversorgung
DAHTA309	Korczak D; Steinhauser G; Dietl M	2011	Prävention des Alkoholmissbrauchs von Kindern, Jugendlichen und jungen Erwachsenen
DAHTA255	Balzer K; Bremer M; Schramm S; Lühmann D; Raspe H	2012	Sturzprophylaxe bei älteren Menschen in ihrer persönlichen Wohnumgebung
DAHTA281	Hagen A; Gorenoi V; Schönermark MP	2012	Knochenersatzmaterialien zur Behandlung von traumatischen Frakturen der Extremitäten
DAHTA307	Aidelsburger P; Schauer S; Grabein K; Wasem J	2012	Alternative Methoden zur Behandlung postmenopausaler Beschwerden
DAHTA329	Neusser S; Bitzer EM; Mieth I; Krauth C	2012	Medizinische Wirksamkeit und Kosteneffektivität von Minocyclin/Rifampicin-beschichteten zentralvenösen Kathetern zur Prävention von Blutbahninfektionen bei Patienten in intensivmedizinischer Betreuung
DAHTA331	Korczak D; Steinhauser G; Kuczera C	2012	Effektivität der ambulanten und stationären geriatrischen Rehabilitation bei Patienten mit der Nebendiagnose Demenz
DAHTA332	Korczak D; Wastian M; Schneider M	2012	Therapie des Burnout-Syndroms

Table S3: Technology reports with economic assessment based on DAM (n=17); included

Document Number	Authors	Year	Titel
DAHTA024	Aidelsburger P; Hessel F; Wasem J	2003	Stellenwert von Ultraschallverfahren im Rahmen der Osteoporoseversorgung (Früherkennung des Frakturrisikos). Ökonomischer Kurz-HTA
DAHTA067	Siebert U; Muth C; Sroczynski G; Velasco-Garrido M; Gerhardus A; Gibis B	2003	Dünnschichtpräparationen und computergestützte Untersuchungen von Zervixabstrichen - Medizinische Effektivität, gesundheitsökonomische Evaluation und systematische Entscheidungsanalyse
DAHTA069	Siebert U; Sroczynski G	2003	Antivirale Therapie bei Patienten mit chronischer Hepatitis C in Deutschland - medizinische und ökonomische Evaluation der initialen Kombinationstherapie mit Interferon / Peginterferon und Ribavirin
DAHTA071	Corzillius M; Mühlberger N; Sroczynski G; Peeters J; Siebert U; Jäger H; Wasem J	2003	Wertigkeit des Einsatzes der genotypischen und phänotypischen HIV-Resistenzbestimmung im Rahmen der Behandlung von HIV-infizierten Patienten
DAHTA063	Kunze S; Schnell-Inderst P; Hessel F; Grill E; Nickisch A; Siebert U; Voß von H; Wasem J	2004	Hörscreening für Neugeborene - ein Health Technology Assessment der medizinischen Effektivität und der ökonomischen Effizienz
DAHTA110	Frank W; Konta B; Peters-Engl C	2004	Pap-Test zum Screening auf Zervixkarzinom. Einfluss verschiedener Untersuchungsintervalle
DAHTA126	Gorenoi V; Dintsios CM; Hagen A	2005	Senkung der Restenoserate durch Einsatz beschichteteter Stents bei koronarer Herzkrankheit. Systematische Übersicht zur medizinischen Wirksamkeit und gesundheitsökonomische Bewertung zum Vergleich von beschichteten gegenüber unbeschichteten Stents
DAHTA131	Zahn J von; Schnell-Inderst P; Gothe H; Häussler B; Menke D; Brüggenjürgen B; Willich S; Wasem J	2006	Episiotomie bei der vaginalen Geburt
DAHTA137	Schnell-Inderst P; Kunze S; Hessel F; Grill E; Siebert U; Nickisch A; Voss H von; Wasem J	2006	Hörscreening für Neugeborene - Update
DAHTA148	Gorenoi V; Dintsios CM; Schönermark MP; Hagen A	2006	Laparoskopische vs. offene Appendektomie - Systematische Übersicht zur medizinischen Wirksamkeit und gesundheitsökonomische Analyse
DAHTA193	Siebert U; Bornschein B; Schnell-Inderst P; Rieber J; Pijls N; Wasem J; Klauss V	2008	Messung der fraktionierten Flussreserve zur Indikationsstellung der perkutanen Koronarintervention
DAHTA218	Gorenoi V; Dintsios CM; Schönermark MP; Hagen A	2008	Intravaskuläre Brachytherapie bei peripherer arterieller Verschlusskrankheit (PAVK)
DAHTA219	Gorenoi V; Dintsios CM; Schönermark MP; Hagen A	2008	Medikamente freisetzende Stents im Vergleich zu Bypass-Operationen bei koronarer Herzkrankheit
DAHTA229	Schmieder K; Engelhardt M; Wawrzyniak S; Börger S; Becker K; Zimolong A	2010	Stellenwert der Radiochirurgie von Meningeomen im Vergleich mit der fraktionierten stereotaktischen Bestrahlung, der konventionellen 3D-geplanten konformalen Bestrahlung und der mikrochirurgischen Operation
DAHTA265	Sroczynski G; Schnell-Inderst P; Mühlberger N; Lang K; Aidelsburger P; Wasem J; Mittendorf T; Engel J; Hillemanns P; Petry KU; Krämer A; Siebert U	2010	Entscheidungsanalytische Modellierung zur Evaluation der Langzeit-Effektivität und Kosten-Effektivität des Einsatzes der HPV-DNA-Diagnostik im Rahmen der Zervixkarzinomfrüherkennung in Deutschland
DAHTA297	Gorenoi V; Schönermark MP; Hagen A	2011	Perkutane Koronarinterventionen zusätzlich zur optimalen medikamentösen Therapie bei stabiler Angina Pectoris
DAHTA308	Gorenoi V; Schönermark MP; Hagen A	2012	CT-Koronarangiografie versus konventionelle invasive Koronarangiografie bei der KHK-Diagnostik

Table S4: Technology reports without economic assessment (n=31); excluded

Document Number	Authors	Year	Titel
DAHTA002	Lühmann D; Kohlmann T; Raspe H	1998	Die Evaluation von Rückenschulprogrammen als medizinische Technologie
DAHTA003	Gibis B; Busse R; Reese E; Richter K; Schwartz FW; Köbberling J	1998	Das Mammographie-Screening zur Brustkrebsfrüherkennung
DAHTA005	Pientka L	1998	PSA-Screening beim Prostatakarzinom
DAHTA006	Gibis B; Busse R; Schwartz FW	1999	Verfahrensbewertung der Magnet-Resonanz-Tomographie (MRT) in der Diagnostik des Mamma-Karzinoms
DAHTA007	Pientka L	1999	Minimal-invasive Therapie der benignen Prostatahyperplasie (BPH-Syndrom)
DAHTA008	Röseler S; Duda L; Schwartz FW	1999	Evaluation präoperativer Routinediagnostik (Röntgenthorax, EKG, Labor) vor elektiven Eingriffen bei Erwachsenen
DAHTA011	Perleth M; Jakubowski E; Busse R	1999	Bewertung von Verfahren zur Diagnostik der akuten Sinusitis maxillaris bei Erwachsenen
DAHTA012	Gernreich C	1999	Spezifische Hyposensibilisierung mit Allergenextrakten bei extrinsischem Asthma bronchiale und Insektengiftallergie
DAHTA013	Lühmann D; Kohlmann T; Lange S; Raspe H	2000	Die Rolle der Osteodensitometrie im Rahmen der Primär-, Sekundär- und Tertiärprävention/Therapie der Osteoporose
DAHTA014	Röseler S; Schwartz FW	2000	Evaluation arthroskopischer Operationen bei akuten und degenerativen Meniskusläsionen
DAHTA015	Fritze J	2000	Die Evaluation von Stroke Units als medizinische Technologie
DAHTA017	Perleth M	2000	Vergleichende Effektivität und Differentialindikation von Ballondilatation (PTCA) versus Bypasschirurgie bei Ein- und Mehrgefäßerkrankungen der Herzkranzgefäße
DAHTA018	Lühmann D; Hauschild B; Raspe H	2000	Hüftgelenkendoprothetik bei Osteoarthrose
DAHTA004	Droste S; Brand A	2001	Biochemisches Screening für fetale Chromosomenanomalien und Neuralrohrdefekte - eine Verfahrensbewertung
DAHTA022	Lühmann D	2001	Stellenwert der Magnet-Resonanz-Tomographie im Rahmen der Versorgung von Patienten mit Rückenschmerzen - Kurz-HTA: Update einer Best-Evidence-Synthese
DAHTA061	Corzillius M; Pientka L; Siebert U; Wasem J	2002	Wertigkeit von Tumor-Nekrose-Faktor alpha-Antagonisten in der Behandlung der rheumatoiden Arthritis (Medizinischer Teil)
DAHTA068	Gorenoi V; Dintsios CM; Perleth M	2002	Stenting versus Ballondilatation bei koronarer Herzkrankheit - systematische Übersicht zur medizinischen Effektivität
DAHTA010	Lühmann D; Raspe H	2003	Operative Eingriffe an der lumbalen Wirbelsäule bei bandscheibenbedingten Rücken- und Beinschmerzen - eine Verfahrensbewertung
DAHTA026	Dettenkofer M; Merkel H; Mutter J	2003	Bewertung unterschiedlicher Hygienekonzepte zur Kontrolle von MRSA (Methicillin-resistente Staphylococcus aureus)
DAHTA029	Schroeder A; Reese E; Richter K; Köbberling J	2003	Die Wertigkeit der Streßechokardiographie in der Primärdiagnostik der koronaren Herzkrankheit
DAHTA030	Wild C; Frank W; Konta B; Huber K	2003	Medizinische Effektivität beim Einsatz von GP- IIb / IIIa-Rezeptorantagonisten in der Therapie von akuten Koronarsyndromen
DAHTA060	Perleth M; Gerhardus A; Velasco M	2003	Positronen-Emissions-Tomographie - systematische Übersichten zur Wirksamkeit bei ausgewählten Indikationen
DAHTA065	Peeters J; Siebert U; Aidelsburger P; Regar E; Rieber J; Wasem J; Klauss V	2003	Wertigkeit des Einsatzes der intravaskulären Ultraschallbildgebung (IVUS) im Rahmen von diagnostischen und therapeutischen Herzkatheteruntersuchungen - ein HTA-Bericht zur medizinischen Effektivität
DAHTA073	Mand P	2003	Verfahrensbewertung der CT-Angiographie, MR-Angiographie, Doppler-Sonographie und Szintigraphie bei der Diagnose von Nierenarterienstenosen
DAHTA078	Gernreich NC; Gerhardus A; Velasco-Garrido M	2003	Knochen- und Knochenersatzmaterialien zur parodontalen Regeneration und zum Knochenaufbau für Implantate - eine systematische Bewertung der medizinischen Wirksamkeit
DAHTA072	Rosery H; Maxion-Bergemann S; Rosery B; Bergemann R	2004	Ultraschall in der Schwangerschaft. Beurteilung der routinemäßigen Schwangerschaftsultraschalluntersuchungen unter Maßgabe der Mutterschaftsrichtlinien
DAHTA074	Schroeder A; Heiderhoff M; Köbberling J	2004	Stroke Units - Update des HTA Berichts "Die Evaluation von Stroke Units als medizinische Technologie"
DAHTA113	Schroeder A; Heiderhoff M; Köbberling J	2005	Bestimmung der Albuminausscheidung im Urin bei Diabetikern zur Vorsorge und Kontrolle der diabetischen Nephropathie
DAHTA117	Lange-Lindberg AM; Velasco-Garrido M; Busse R	2006	Misteltherapie als begleitende Behandlung zur Reduktion der Toxizität der Chemotherapie maligner Erkrankungen
DAHTA233	Rasch A; Müller-Riemenschneider F; Vauth C; Willich SN; Greiner W	2008	Föderale Strukturen und damit verbundene verhaltensbezogene Maßnahmen zur Prävention des Zigarettenrauchens
DAHTA344	Korczak D	2012	Föderale Strukturen der Prävention von Alkoholmissbrauch bei Kindern und Jugendlichen

Table 5: Methodological reports (n=20); excluded

Document Number	Authors	Year	Titel
DAHTA1	Bitzer E; Busse R; Dörning H; Duda L; Köbberling J; Kohlmann T; Lühmann D; Pasche S; Perleth M; Raspe H; Reese E; Richter K; Röseler S; Schwartz FW	1998	Bestandsaufnahme, Bewertung und Vorbereitung der Implementation einer Datensammlung "Evaluation medizinischer Verfahren und Technologien" in der Bundesrepublik
DAHTA9	Behrend C; Greiner W; Hessel F; Hoffmann C; Leidl R; Mühlberger N; Schulenburg JM Graf von der; Siebert U; Wasem J; Welte R	1999	Ansätze und Methoden der ökonomischen Evaluation - eine internationale Perspektive
DAHTA25	Raum E; Perleth M	2003	Methoden der Metaanalyse von diagnostischen Genauigkeitsstudien
DAHTA27	Aidelsburger P; Felder S; Siebert U; Wasem J	2003	Gesundheitsökonomische "Kurz-HTA-Berichte" - eine systematische Übersichtsarbeit zur Methodik und Implementation
DAHTA34	Ekkernkamp M; Lühmann D; Raspe H	2003	Methodenmanual für "HTA-Schnellverfahren" und Exemplarisches "Kurz-HTA": Die Rolle der quantitativen Ultraschallverfahren zur Ermittlung des Risikos für osteoporotische Frakturen
DAHTA62	Droste S; Gerhardus A; Kollek R	2003	Methoden zur Erfassung ethischer Aspekte und gesellschaftlicher Wertvorstellungen in Kurz-HTA-Berichten - eine internationale Bestandsaufnahme
DAHTA122	Zentner A; Velasco-Garrido M; Busse R	2005	Methoden zur vergleichenden Bewertung pharmazeutischer Produkte
DAHTA99	Siebert U	2005	Entscheidungsanalytische Modelle zur Sicherung der Übertragbarkeit internationaler Evidenz von HTA auf den Kontext des deutschen Gesundheitssystems
DAHTA31	Gerhardus A; Dintsios CM	2006	Der Einfluss von HTA-Berichten auf die gesundheitspolitische Entscheidungsfindung - eine systematische Übersichtsarbeit
DAHTA210	Neumann U; Hagen A; Schönermark MP	2007	Regulation der Aufnahme von innovativen nichtmedikamentösen Technologien in den Leistungskatalog solidarisch finanzierter Kostenträger
DAHTA194	Siebert U; Zietemann V; Sroczynski G	2008	Pharmacogenomics-Bias - Systematische Verzerrungen in Studienergebnissen durch genetische Heterogenität
DAHTA214	Kossmann B; Ulle T; Kahl KG; Wasem J; Aidelsburger P	2008	Nichtmedikamentöse verhaltensbezogene Adipositastherapie unter Berücksichtigung der zugelassenen Arzneimittelbehandlung
DAHTA243	Schöttker B; Lühmann D; Boulkhemair D; Raspe H	2009	Indirekte Vergleiche von Therapieverfahren
DAHTA250	Mangiapane S; Velasco Garrido M	2009	Surrogatendpunkte als Parameter der Nutzenbewertung
DAHTA251	Gorenoi V; Schönermark MP; Hagen A	2009	Instrumente zur Risikoprädiktion für kardiovaskuläre Erkrankungen
DAHTA259	Gorenoi V; Schönermark MP; Hagen A	2009	Gelenkendoprothesenregister für Deutschland
DAHTA272	Bartelmes M; Neumann U; Lühmann D; Schönermark MP; Hagen A	2009	Methoden zur frühen entwicklungsbegleitenden Bewertung innovativer medizinischer Technologien
DAHTA260	Dreier M; Borutta B; Stahmeyer J; Krauth C; Walter U	2010	Vergleich von Bewertungsinstrumenten für die Studienqualität von Primär- und Sekundärstudien zur Verwendung für HTA-Berichte im deutschsprachigen Raum
DAHTA264	Gorenoi V; Schönermark MP; Hagen A	2010	Infektionsschutz in der Knieendoprothetik
DAHTA220	Brettschneider C; Lühmann D; Raspe H	2011	Der Stellenwert von Patient-Reported Outcomes (PRO) im Kontext von Health Technology Assessment (HTA)

Article 9

Cost effectiveness of elderly pneumococcal vaccination in presence of higher-valent pneumococcal conjugate childhood vaccination: systematic literature review with focus on methods and assumptions

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SYSTEMATIC REVIEW

Cost Effectiveness of Elderly Pneumococcal Vaccination in Presence of Higher-Valent Pneumococcal Conjugate Childhood Vaccination: Systematic Literature Review with Focus on Methods and Assumptions

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Abstract

Background Previous systematic reviews concluded that pneumococcal vaccination in the elderly was cost effective. However, recently published economic evaluations state that it may not be cost effective when children are vaccinated with higher-valent pneumococcal conjugate vaccines. The literature suggests that the outcomes of vaccination in the elderly are strongly influenced by the vaccine effectiveness (VE) against the vaccine-type pneumococcal diseases (PD) and the impact of childhood vaccination on the vaccine-type PD incidence in the elderly, but the extent remains unclear.

Methods We conducted a systematic literature search of cost-effectiveness studies on vaccination in the elderly in the PubMed database starting from 2006. We included studies that consider the presence of a childhood vaccination with pneumococcal conjugate vaccine (PCV) 10 and PCV13. We focus on methods and assumptions used in modeling VE and epidemiology of PD over time.

Results Twenty-eight economic evaluations underwent full-text review and data extraction. Thirteen were selected for quality assessment. The studies with a higher quality score provide evidence that vaccinating the elderly with PCV13 is not cost effective, when an ongoing rapid decline in the incidence of PCV13-type PD is modeled. A moderate persistence of PCV13 serotypes, in particular due to PCV10 childhood vaccination, makes vaccination of the elderly with PCV13 more attractive. There is no agreement that combining PCV13 with polysaccharide vaccine PPSV23 is cost effective. PPSV23 is attractive when it is effective against non-invasive PD.

Conclusion Methodological approaches and assumptions in modeling VE and the indirect effects of childhood vaccination have a major impact on outcomes of decision-analytic models and cost-effectiveness estimates. Considering recently observed trends in the epidemiology of pneumococcal serotypes, there is currently inconclusive evidence regarding the cost effectiveness of pneumococcal vaccination of the elderly due to lack of studies that model key serotypes such as serotype 3 separately from other groups of serotypes.

1 Introduction

Vaccination of susceptible groups is the most effective measure to fight diseases caused by *Streptococcus pneumoniae* (*S. pneumoniae*) on a population level. Pneumococcal conjugate vaccination of infants and young children has been established in many developed countries and indisputably has proven to be an effective preventive measure [1]. Following the 7-valent pneumococcal conjugate vaccine (PCV7), the introduction of higher valent conjugate vaccines (PCV10 and PCV13) has further reduced the burden of the pneumococcal diseases (PD) [1, 2]. The vaccination of the elderly in the presence of routine childhood vaccination with the higher valent pneumococcal conjugate vaccines (PCVs) still poses questions on general cost effectiveness, optimal age of vaccine administration, and which vaccine should be

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Key Points for Decision Makers

Understanding of the methods and assumptions to model the vaccine effects and predict epidemiology of pneumococcal diseases can help to rationally interpret obtained conclusions about the cost effectiveness of pneumococcal vaccination in the elderly.

It is important to look at the modeling of the key factors that majorly drive the outcomes of the vaccination; these include the applied vaccine effectiveness, the assumptions about the waning of vaccine protection, the prior-vaccination incidence of invasive and non-invasive pneumococcal diseases in the targeted population, and the indirect impact of the childhood pneumococcal vaccination with higher valent pneumococcal conjugate vaccines on the epidemiology of the diseases.

Due to the country-specific differences in the major economic factors (e.g., vaccination strategy, vaccine price, cost per disease case and discount rates) and epidemiological patterns, any comparisons between the outcomes of the different economic evaluations should be made with caution.

used. Conclusions of previously published systematic literature reviews [3–6] suggest that the polysaccharide vaccine PPSV23 and the conjugate vaccine PCV13 can be considered cost effective for vaccinating the elderly against pneumococcal diseases. Ogilvie et al. [3] reviewed 11 economic evaluations of vaccination of the elderly with PPSV23 and concluded that the vaccination could be cost effective compared with no program for individuals older than 65 years. These findings were supported by Nishikawa et al. [5] in a recently published review. Dirmesropian et al. [4] reviewed ten economic evaluations of usage of PCV13 in adults and the elderly and concluded that the conjugate vaccine was also cost effective [4]. However, the authors stated that the drawn estimates of the cost effectiveness should be interpreted with caution in respect to key factors that influenced the cost effectiveness, which were uncertain at that time. These included the effectiveness of PCV13 against invasive pneumococcal diseases (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) in the elderly, the effectiveness of PPSV23 and the indirect effects of higher-valent PCV childhood immunization programs on the epidemiology of PD in the elderly [4].

Since the publication of the review by Dirmesropian et al. [4], new clinical evidence on PCV13 effectiveness against IPD and NBPP in the elderly has been generated in the CAPiTA trial (Community-Acquired Pneumonia Immunization Trial in Adults) [7]. CAPiTA has become a milestone in the current debates and triggered reassessments of cost effectiveness of PCV13 versus PPSV23 in view of its findings. Recently, Porchia et al. [6] conducted a review of 31 economic evaluations including the studies that informed the parameters based on the CAPiTA findings [7]. The authors concluded that both PPSV23 and PCV13 programs in the elderly were cost-effective and should be seen as a priority by decision makers [6]. Although the authors conducted a substantial review of the economic parameters, they did not address the uncertainty around vaccine effectiveness (VE) and epidemiological changes in pneumococcal diseases originated from the childhood vaccination with PCV13 and/or PCV10. By doing so, in our opinion, the authors limited their summarization of the current evidence for decision makers. In addition, since their publication a number of economic evaluations have been published that concluded that under the influence of the herd effect induced by childhood vaccination with a higher valent conjugate vaccine, vaccination of the elderly was unlikely to be cost effective [8–10].

In contrast to Porchia et al. [6], we investigated the cost effectiveness of vaccination strategies for the elderly in the presence of childhood pneumococcal vaccination with PCV10 and PCV13. We focus on the methods, assumptions, and data used to model the vaccine effects in order to ensure that input VE was consistent with the current knowledge and that potential epidemiological effects stemming from the childhood vaccination were not neglected or oversimplified.

2 Methods

2.1 Constituents of Vaccination Effects

The direct outcomes of a pneumococcal vaccination campaign in the elderly are determined by VE in preventing PD caused by the serotypes contained in the pneumococcal vaccine (and cross-protective serotypes [11]) as well as the disease incidence in the targeted population.

2.1.1 Vaccine Effectiveness Among the Elderly

The pneumococcal vaccine protection is expected to decline over time. PPSV23 protection has been shown to wane during and also after the first 5 years [12–15]. PCV13 is thought to provide longer protection than PPSV23 because it triggers a stronger immune response [16]. The CAPiTA results [7] show that PCV13 protection is stable over 4–5 years but its waning is still uncertain [11, 17]. Therefore, overall VE over the period of its protection can be composed of the initial VE at the time of administration and a waning pattern (see electronic supplementary material [ESM] file S1). We used the initial VE at administration and the waning of the vaccine

protection reported in the studies to plot the decline of VE over time and to calculate the area under the resulting curve. This area under the curve represents the expected vaccine protection over time (EVPOT); that is, integration of the years of protection adjusted for VE at a given point in time (see ESM file S1: section 1.1). We applied a cut-off point of 20 years since vaccination when a longer period of waning was assumed. The expected vaccine protection over time is measured in efficacy-adjusted protection years (EAPY) and enables a comparative analysis of the assumptions about VE and duration of protection across the studies.

2.1.2 Incidence of Disease Due to *S. pneumoniae* Among the Elderly

Currently, over 90 different strains (serotypes) of *S. pneumoniae* have been identified, with certain strains having a higher potential to cause the disease and a higher prevalence in the susceptible groups [18]. The currently available pneumococcal vaccines contain a limited number of the serotypes; that is, PCV13 covers 13 antigens and PPSV23 includes the PCV13 serotypes, except for serotype 6A, and 11 additional antigens. Therefore, in the case of *S. pneumoniae*, VE could be interpreted as the proportionate reduction in occurrence of the disease caused only by the strains contained in this vaccine and included as such in the cost-effectiveness analyses.

In addition, in the countries where children are routinely vaccinated with PCV, childhood vaccination has indirect effects on pneumococcal infection caused by the vaccine strains among the elderly. The observed indirect effects include the herd effect (i.e., the indirect reduction in vaccine-type disease incidence as an effect of the childhood vaccination) and replacement disease (i.e., an indirect increase in non-vaccine-type PD incidence) [1]. The type of PCV vaccine (PCV7, PCV10, or PCV13) implemented in the infant vaccination programs plays a crucial role in the evolution of vaccine-type PD incidence among the elderly. Furthermore, the sequence of PCV infant vaccination programs (for instance PCV7 replaced by PCV13 or PCV7 followed by PCV13 and then PCV10) can also have an impact on the cost effectiveness of pneumococcal vaccination of the elderly.

Therefore, the vaccine-type PD incidence in the target population over time is determined by vaccine-serotype disease incidence before the implementation of the PCV childhood vaccination and the indirect effects on the epidemiology of *S. pneumonia* in this population. The key factors that determine the performance of the elderly pneumococcal vaccination, are illustrated in Fig. 1 and are described in greater detail in the ESM (file S1: section 1). Due to the complex dynamics seen in the strains of *S. pneumonia*, an accurate projection of vaccine-type PD incidences is challenging and subject to major assumptions. Therefore, we reviewed the assumptions and methodological choices applied in the modeling of vaccine-type IPD and NBPP incidences.

2.2 Review Strategy

We conducted an extensive search in the PubMed database to find studies for full-text review. The identified studies were subject to the full-text review with data extraction and selection for the following assessment of quality of economic evaluation. The search syntax, inclusion criteria for the full-text review and data extraction are described in the ESM (file S1: section 2). In accordance with the goal of this review, we defined inclusion criteria for the assessment of quality of the selected studies as follows:

1. VE parameters are obtained (i) for PCV13—from or based on the CAPiTA trial [7]; (ii) for PPSV23—from a meta-analysis, a randomized clinical trial (RCT) or an observational study. These criteria are in accordance with the guidelines of the World Health Organization (WHO) for economic evaluations of vaccination programs [19].
2. Childhood pneumococcal conjugate vaccination with the higher-valent vaccines is included in baseline scenarios. Post-PCV data are used to project the burden of pneumococcal diseases in the targeted population.

Quality of economic evaluations of the studies that met both selection criteria was assessed using the "Evidence and Value: Impact on DEcisionMaking" (EVIDEM) instrument: "assessment of quality of economic evaluations" [20]. In compliance with the EVIDEM instrument, we developed a form consisting of two parts: (i) completeness and consistency of reporting of economic evaluation, and (ii) relevance and validity of economic evaluation. The instrument allowed a sequential and structured assessment of economic evaluations across 11 dimensions and provided a way of transparent reporting ensuring full traceability of the reviewers' work. We placed a particular focus on completeness, consistency and relevance of the assumptions and methods applied in modeling VE and the indirect effects of the childhood PCV vaccination. Two evaluators (MT, SMS) selected the studies and independently completed the developed form and assigned a score (between one for low and four for high relevance/validity) for each study with a summarizing rationale for the given score. The decisions were compared, and any disagreement was resolved under arbitration by the third reviewer (AK). The studies excluded from the assessment of quality are summarized in the ESM, including the reason for their exclusion.

The assessed economic evaluations were further summarized in a comparative analysis of the assumptions and

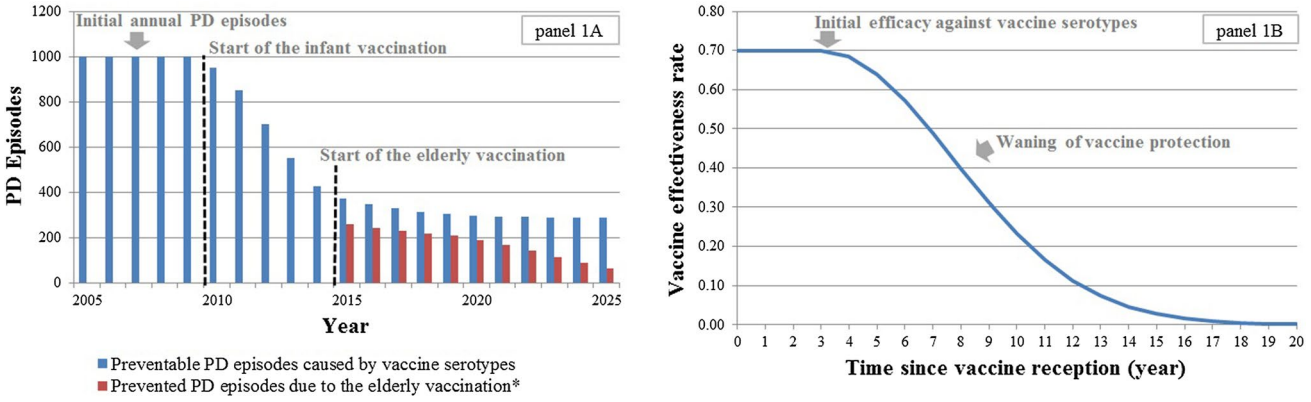

Fig. 1 Constituents of the vaccination effects over time: a graphical representation. The outcomes of the elderly pneumococcal vaccination depend on the initial vaccine effectiveness against vaccine-type PD and its protection over time (illustrated in **b**) and the PD incidence caused by vaccine-type serotypes over time, which is also influenced by the indirect effects of a childhood vaccination with PCV (illustrated in **a**). Asterisk: vaccination rate 100% and vaccine effectiveness according to **b**. *PD* pneumococcal diseases

the methods applied to model the VE among the elderly, the incidence of invasive and non-invasive diseases due to *S. pneumoniae*, and the indirect effects of the vaccination programs with higher valent conjugate vaccines in children on the PD incidence in the elderly population. Thereafter, the cost effectiveness of the elderly vaccination programs was described using the findings of the studies that were evaluated with an EVIDEM score of three or higher for relevance and validity of economic evaluation. To facilitate the comparison of incremental cost-effectiveness ratio (ICER) estimates between the studies, the reported ratios were firstly time-adjusted to the year 2017 by applying the country-specific consumer price indices from the organisation for economic co-operation and development (OECD) [21]. Afterwards, the 2017 country-specific values were standardized to 2017 US dollars using the purchasing power parity (PPP) index [22] and exchange rates for 2017 from the OECD [23].

3 Results

3.1 Literature Search and Selection

The search was conducted on 18 October 2017 and updated twice on 2 March 2018 and 28 May 2018 to identify recently published studies. Overall, it resulted in 28 studies selected for the full-text review (see Fig. 2). Of these, 13 economic evaluations were selected for the assessment of quality [8–10, 24–33], and the remaining 15 studies [34–46] were excluded from further analysis and are summarized in the ESM (file S2).

The extracted data from the selected studies are summarized in three tables. Table 1 gives the extracted data on base-case VE parameters and calculated EVPOT; Table 2 gives an overview of the applied methods and the quality assessment scores of the economic evaluations; and Table 3 describes the main characteristics of the health economic evaluations, the reported ICERs, and the conclusions given in the evaluations. The sources for VE cited in the reviewed studies as well as the extracted incidence rates with their sources are summarized in the ESM (files S3 and S4, respectively). The results of the quality assessment of economic evaluation with EVIDEM are given in the ESM (file S5).

3.2 Assumptions and Methods Used to Model the Vaccine Effects Over Time

3.2.1 Initial Vaccine Effectiveness

Although we included only the evaluations that had obtained the initial PCV13 VE from the CAPiTA trial [7], the reported values varied between the studies (see Table 1). For instance, in the age group 65–74 years, the average initial PCV13 VE against IPD ranged from 75 to 84.5%. The main reasons for this variation are methodological differences in the application of vaccine-age-interaction effects and in the estimates of effect of age on the initial VE. Eight [8–10, 25, 27, 30, 31, 33] of 12 studies (which evaluated PCV13) applied age-interaction effects of the initial VE. Of them, five studies [8–10, 25, 30] derived estimates of the vaccine-age-interaction effect from a post-hoc analysis of the CAPiTA data [50, 51] (see Table 2). Another study [33] assumed that the age-vaccine-interaction effect for PCV13 is 50% lower than the effect for PPSV23. Two studies [27, 31] applied age-group-specific variations of the initial PCV13 VE. Heo et al. [31] adjusted VE assumptions by Smith et al. [40]. Rodriguez Gonzalez-Moro et al. [27] did not describe the methods for the calculation of age-group-specific VE parameters.

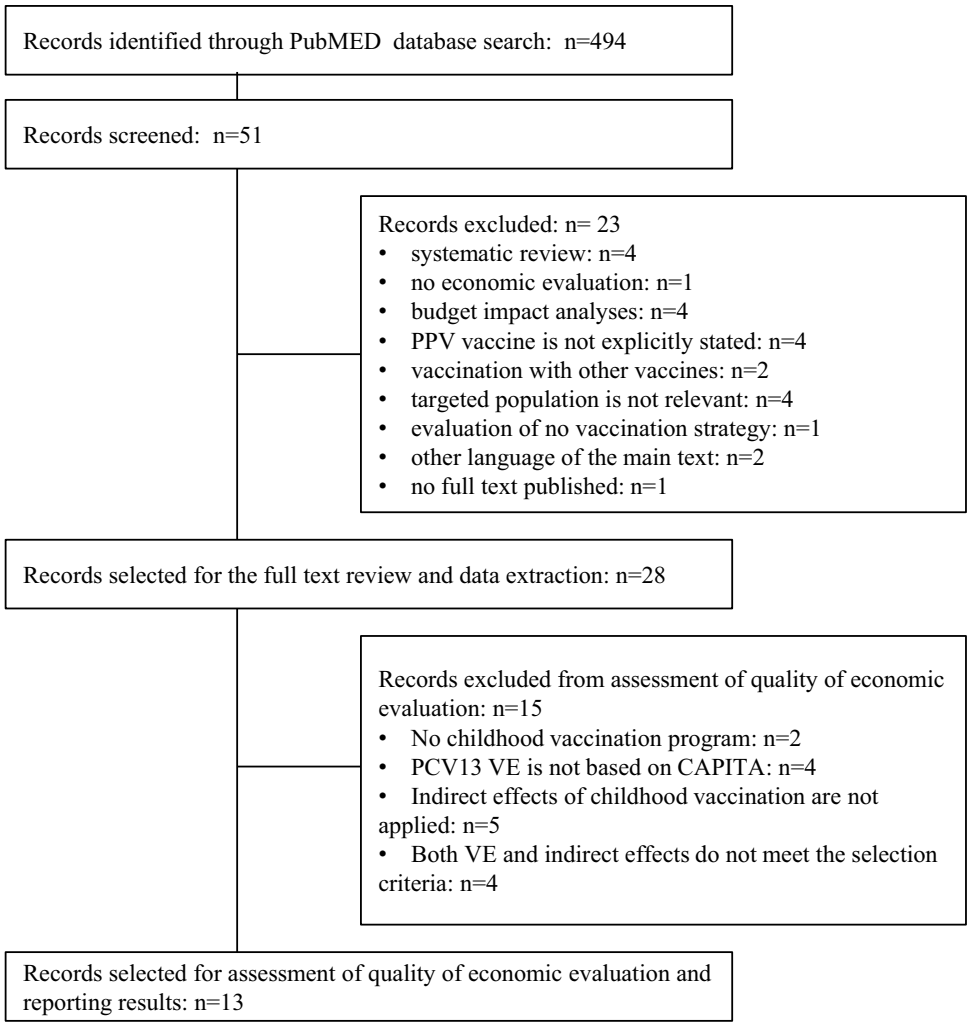

Fig. 2 Literature search, study inclusion, and selection for the assessment of quality of economic evaluation. *PPV* pneumococcal polysaccharide vaccine, *VE* vaccine effectiveness

We found a great variation in the applied values of the initial PPSV23 VE with two major sources of the variation of the VE values: the application of the vaccine-age-interaction effects and sources of the initial VE (see Tables 1, 2). In the age group 65–74 years, the average PPSV23 VE against IPD ranged from 55 to 82% (see Table 1). In eight studies [8, 9, 26–28, 30, 31, 33], PPSV23 VE against NBPP was assumed to be 0% based on the findings of several reviews and observational studies [53, 54, 59, 60] (see Table 2 for VE sources). Three studies applied VE of 39% [24], 30.8% [10], and 19.6% [32] based on other empirical studies [48, 57]. Four studies [27, 30, 31, 33] applied vaccine-age-interaction effects for PPSV23. Only Kuchenbecker et al. [33] and Dirmesropian et al. [30] reported single-age-specific initial VE for PPSV23. Dirmesropian et al. [30] applied a logistic function that was calibrated for ≥75 year-olds based on data from the study by Andrews et al. [15]. Kuchenbecker et al. [33] calculated the initial PPSV23 VE using a linear interpolation of VE estimates for 50-, 65- and 80-year-olds reported by Smith et al. [61]. In order to facilitate comparison of the initial VE assumptions between the studies, we defined four age groups and reported the extracted VE values in Table 1 according to these groups. For the studies that apply functions to calculate VE, Table 1 gives the unweighted average.

3.2.2 Vaccine Protection Over Time

Figure 3 gives an overview of the protection waning patterns among the reviewed evaluations. Applied waning patterns varied in their structure and, hence, showed different shapes of the curves. It resulted in differences of the calculated expected vaccine protection over time. The most common waning pattern included a period of stable VE followed by a step-wise linear decline of VE to 0% [8, 9, 25, 29, 30, 32, 33]. Three studies [27, 28, 31] applied age-group-specific waning patterns and one study [33] used single-age-specific patterns. We calculated EVPOT for the generic age groups to enable comparison between the studies. Figure 4 shows the resulting values. In this section we focus on the resulting EVPOT for immunocompetent people aged 65–74 years. For

Table 1 Initial vaccine effectiveness and expected vaccine protection over time ($n = 13$)

Risk group	Study	PCV13								PPSV23							
		Against IPD				Against NBPP				Against IPD				Against NBPP			
		50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years
Initial vaccine effectiveness (%)																	
IC	Jiang et al., 2012, Germany [24]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	74.00	74.00	74.00	74.00	39.00	39.00	39.00	39.00
	Mangen et al., 2015, Netherlands [25]	92.14[a]	83.11[a]	68.82[a]	57.44[a]	72.54[a]	56.57[a]	37.31[a]	24.03[a]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Blommaert et al., 2016, Belgium [26]	75.00	75.00	75.00	75.00	41.10	41.10	41.10	41.10	55.00	55.00	55.00	55.00	0.00	0.00	0.00	0.00
	Rodriguez Gonzalez-Moro et al., 2016, Spain [27]	82.00	76.80	72.20	67.60	48.97	45.88	43.30	40.72	87.30	76.60	67.80	59.40	0.00	0.00	0.00	0.00
	Stoecker et al., 2016, USA [28]	75.00	75.00	75.00	75.00	45.00	45.00	45.00	45.00	74.00	74.00	74.00	74.00	0.00	0.00	0.00	0.00
	van Hoek and Miller, 2016, England [29]	75.00	75.00	75.00	75.00	45.60	45.60	45.60	45.60	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Dirmesropian et al., 2017, Australia [30]	n/a	84.50[a]	67.16[a]	20.26[a]	n/a	50.19[a]	18.87[a]	0.00[a]	n/a	58.00[a]	55.51[a]	5.53[a]	n/a	0.00	0.00	0.00
	Heo et al., 2017, Korea [31]																
	Low risk	79.40	75.00	62.80	62.80	52.00	45.00	37.70	37.70	95.30	82.00	68.70	68.70	0.00	0.00	0.00	0.00
	High risk	67.49	63.75	53.38	53.38	41.60	36.00	30.16	30.16	76.24	65.60	54.96	54.96	0.00	0.00	0.00	0.00
	Chen et al., 2018, Australia [8, 9]	n/a	84.50[a]	67.16[a]	20.26[a]	n/a	50.19[a]	18.87[a]	0.00	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Thorrington et al., 2018, Netherlands [32]	75.00	75.00	75.00	75.00	38.00	38.00	38.00	38.00	62.00	62.00	62.00	62.00	19.60	19.60	19.60	19.60
	Willem et al., 2018, Belgium [10]	75.80[b]	75.80[b]	75.80[b]	0.00	41.10[b]	41.10[b]	41.10[b]	0.00	56.00	56.00	56.00	0.00	30.80	30.80	30.80	0.00
	Kuchenbecker et al., 2018, Germany [33]	81.93[a]	76.52[a]	72.83[a]	68.89[a]	48.47[a]	45.76[a]	43.92[a]	41.94[a]	86.93[a]	76.10[a]	68.73[a]	60.85[a]	0.00	0.00	0.00	0.00

Table 1 (continued)

Risk group	Study	PCV13								PPSV23							
		Against IPD				Against NBPP				Against IPD				Against NBPP			
		50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years
IS	Jiang et al., 2012, Germany [24]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	35.00	35.00	35.00	35.00	0.00	0.00	0.00	0.00
	Mangen et al., 2015, Netherlands [25]	71.87[a]	64.83[a]	53.68[a]	44.80[a]	47.15[a]	36.77[a]	24.25[a]	15.62[a]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Heo et al., 2017, Korea [31]	61.93	58.50	48.98	48.98	33.80	29.25	24.51	24.51	23.25	20.00	16.75	16.75	0.00	0.00	0.00	0.00
	Kuchenbecker et al., 2018, Germany [33]	63.91[a]	59.68[a]	56.81[a]	53.73[a]	31.50[a]	29.74[a]	28.55[a]	27.26[a]	13.65[a]	1.58[a]	0.00	0.00	0.00	0.00	0.00	0.00
Expected duration of protection (in years)																	
IC	Jiang et al., 2012, Germany [24]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4.38	4.38	4.38	4.38	4.38	4.38	4.38	4.38
	Mangen et al., 2015, Netherlands[25]	12.15	12.15	12.15	12.15	12.15	12.15	12.15	12.15	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Blommaert et al., 2016, Belgium [26]	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	0.00	0.00	0.00	0.00
	Rodriguez Gonzalez-Moro et al., 2016, Spain [27]	10.65[c]	9.27[c]	7.31[c]	4.72	10.65[c]	9.27[c]	7.31[c]	4.72	5.66[c]	4.70[c]	3.78	2.94	0.00	0.00	0.00	0.00
	Stoecker et al., 2016, USA [28]	19.25[c,d]	16.80[c]	16.80[c]	16.80[c]	19.25[c,d]	16.80[c]	16.80[c]	16.80[c]	7.00	7.00	7.00	7.00	0.00	0.00	0.00	0.00
	van Hoek and Miller, 2016, England [29]	12.53[c]	12.53[c]	12.53[c]	12.53[c]	12.46[c]	12.46[c]	12.46[c]	12.46[c]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Dirmesropian et al., 2017, Australia [30]	n/a	7.50	7.50	7.50	n/a	7.50	7.50	7.50	n/a	3.50	3.50	3.50	n/a	0.00	0.00	0.00
	Heo et al., 2017, Korea [31]	12.61[c]	12.53[c]	5.48	5.48	12.54[c]	12.54[c]	5.47	5.47	8.76	6.51	4.99	4.99	0.00	0.00	0.00	0.00
	Chen et al., 2018, Australia [8, 9]	n/a	7.50	7.50	7.50	n/a	7.50	7.50	7.50	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Thorrington et al., 2018, Netherlands [32]	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
	Willem et al., 2018, Belgium [10]	9.54	9.54	9.54	0.00	9.54	9.54	9.54	0.00	4.20	4.20	4.20	0.00	4.20	4.20	4.20	0.00
	Kuchenbecker et al., 2018, Germany [33]	12.01[d]	11.13[d]	10.38[d]	9.33[d]	12.01[d]	11.13[d]	10.38[d]	9.33[d]	8.35[d]	7.38[d]	6.39[d]	5.38[d]	0.00	0.00	0.00	0.00

Table 1 (continued)

Risk group	Study	PCV13								PPSV23							
		Against IPD				Against NBPP				Against IPD				Against NBPP			
		50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years
IS	Jiang et al., 2012, Germany [24]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4.38	4.38	4.38	4.38	0.00	0.00	0.00	0.00
	Mangen et al., 2015, Netherlands [25]	12.15	12.15	12.15	12.15	12.15	12.15	12.15	12.15	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Heo et al., 2017, Korea [31]	12.61	12.53	5.48	5.48	12.54	12.54	5.47	5.47	8.76	6.51	4.99	4.99	0.00	0.00	0.00	0.00
	Kuchenbecker et al., 2018, Germany [33]	12.01[a]	11.13[a]	10.38[a]	9.33[a]	12.01[a]	11.13[a]	10.38[a]	9.33[a]	9.61	7.25	0.00	0.00	0.00	0.00	0.00	0.00
Expected vaccine protection over time (in efficacy adjusted protection years)																	
IC	Jiang et al., 2012, Germany [24]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	3.24	3.24	3.24	3.24	1.71	1.71	1.71	1.71
	Mangen et al., 2015, Netherlands [25]	11.20[a]	10.10[a]	8.36[a]	6.98[a]	8.81[a]	6.87[a]	4.53[a]	2.92[a]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Blommaert et al., 2016, Belgium [26]	3.75	3.75	3.75	3.75	2.06	2.06	2.06	2.06	2.75	2.75	2.75	2.75	0.00	0.00	0.00	0.00
	Rodriguez Gonzalez-Moro et al., 2016, Spain [27]	8.74[c]	7.12[c]	5.28[c]	3.19	5.22[c]	4.25[c]	3.16[c]	1.92	4.94[c]	3.60[c]	2.56	1.75	0.00	0.00	0.00	0.00
	Stoecker et al., 2016, USA [28]	14.44[c,d]	12.60[c]	12.60[c]	12.60[c]	8.66[c,d]	7.56[c,]	7.56[c,]	7.56[c,]	5.18	5.18	5.18	5.18	0.00	0.00	0.00	0.00
	van Hoek and Miller, 2016, England [29]	9.40[c]	9.40[c]	9.40[c]	9.40[c]	5.68[c]	5.68[c]	5.68[c]	5.68[c]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Dirmesropian et al., 2017, Australia [30]	n/a	6.34[a]	5.04[a]	1.52[a]	n/a	3.76[a]	1.42[a]	0.00	n/a	2.03[a]	1.94[a]	0.19[a]	n/a	0.00	0.00	0.00
	Heo et al., 2017, Korea [31]																
	Low risk	10.01[c]	9.40[c]	3.44	3.44	6.52[c]	5.64[c]	2.06	2.06	8.34	5.34	3.43	3.43	0.00	0.00	0.00	0.00
	High risk	8.51[c]	7.99[c]	2.93	2.93	5.22[c]	4.52[c]	1.65	1.65	6.68	4.27	2.74	2.74	0.00	0.00	0.00	0.00
	Chen et al., 2018, Australia [8, 9]	n/a	6.34[a]	5.04[a]	1.52[a]	n/a	3.76[a]	1.42[a]	0.00	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Thorrington et al., 2018, Netherlands [32]	6.75	6.75	6.75	6.75	3.42	3.42	3.42	3.42	1.55	1.55	1.55	1.55	0.49	0.49	0.49	0.49
	Willem et al., 2018, Belgium [10]	7.23	7.23	7.23	0.00	3.92	3.92	3.92	0.00	2.35	2.35	2.35	0.00	1.29	1.29	1.29	0.00
	Kuchenbecker et al., 2018, Germany [33]	9.84[a]	8.52[a]	7.56[a]	6.43[a]	5.82[a]	5.09[a]	4.56[a]	3.91[a]	7.26[a]	5.61[a]	4.39[a]	3.27[a]	0.00	0.00	0.00	0.00

Table 1 (continued)

Risk group	Study	PCV13								PPSV23							
		Against IPD				Against NBPP				Against IPD				Against NBPP			
		50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years	50–64 years	65–74 years	75–84 years	85–99 years
IS	Jiang et al., 2012, Germany [24]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1.53	1.53	1.53	1.53	0.00	0.00	0.00	0.00
	Mangen et al., 2015, Netherlands [25]	8.73[a]	7.88[a]	6.52[a]	5.44[a]	5.73[a]	4.47[a]	2.95[a]	1.90[a]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Heo et al., 2017, Korea [31]	7.81	7.33	2.68	2.68	4.24	3.67	1.34	1.34	2.04	1.30	0.84	0.84	0.00	0.00	0.00	0.00
	Kuchenbecker et al., 2018, Germany [33]	7.68[a]	6.64[a]	5.90[a]	5.01[a]	3.78[a]	3.31[a]	2.96[a]	2.54[a]	1.31[a]	0.11[a]	0.00	0.00	0.00	0.00	0.00	0.00

EAPY efficacy-adjusted protection years, *IC* immunocompromised, *IPD* invasive pneumococcal diseases, *IS* immunosuppressed, *n/a* not applicable, *NBPP* non-bacteremic pneumococcal pneumonia

[a]Average effectiveness/EAPY in the corresponding age group. Original values are age-specific

[b]Age-specific vaccine efficacy cannot be calculated due to a lack of information. Age-independent efficacy assumptions based on the supplement are given instead

[c]Cut-off point for the calculation was 20 years after vaccination. Without cut-off, values would be higher

[d]Average protection years in the corresponding age group. Original values are age-specific

PPSV23, the calculated EVPOT against IPD ranges from 1.5 to 5.6 EAPY depending on both initial VE parameter and the waning of protection. The commonly applied period of constant protection was 1–5 years. In five studies [8, 9, 26, 30, 32], VE declined to 0% within 5–6 years of vaccination, while in the other four studies [27, 28, 31, 33] there was a (small) protective effect at least until the ninth year after vaccination. EVPOT for PCV13 is commonly larger than for PPSV23 and ranges from 3.8 to 12.6 EAPY due to a longer duration of stable protection and the slower decline of the VE afterwards. Nine [8, 9, 25–27, 30, 32, 33] of the 12 studies that model PCV13 protection apply a 4- to 5-year period of stable vaccine protection. Other assumptions include 9 years of stable protection [29] and a shorter period with waning starting in the second year after the initial vaccine administration [28, 31]. Blommaert et al. [26] is the only study that applied in the base-case scenario an equal duration of protection for PCV13 and PPSV23. Furthermore, the study was unique in assuming an instant drop to 0% VE after a stable period of protection for 5 years.

In the Australian studies, Dirmesropian et al. [30] and Chen et al. [8, 9] applied 5 years of waning after the stable protection. In the studies by Rodriguez Gonzalez-Moro et al. [27], Heo et al. [31], Thorrington et al. [32], and Willem et al. [10], the waning to 0% was modeled over 10 years with different waning rates. Mangen et al. [25] and Kuchenbecker et al. [33] applied a 15-year period of waning to 0%. Van Hoek and Miller [29] and Stoecker et al. [28] assumed remaining PCV13 VE even after year 20, with Stoecker et al. [28] assuming very low waning rates compared with all other studies. Due to the assumptions of a longer period of waning, the resulting EVPOT for the studies by Mangen et al. [25], Kuchenbecker et al.[33], van Hoek and Miller [29], and Stoecker et al. [28] lies above 8.5 EAPY. In contrast, the assumption of no waning period by Blommaert et al. [26] resulted in EVPOT of 3.7 EAPY.

In contrast to the common linear decline of protection over time, Willem et al. [10] applied parametric functions of waning after the period of constant protection; these include logistic waning of PCV13 protection and an exponential decay for PPSV23. The calculation of EVPOT with the reported parameterization of these functions led to values similar to other studies: PCV13 against IPD of 7.2 EAPY and PPSV23 against IPD of 2.3 EAPY. The duration of vaccine protection against non-invasive PD was modeled analogously with the lower initial VE. The EVPOT values range from 2.1 to 7.6 EAPY.

3.2.3 Modeling Incidence Over Time (Indirect Herd and Replacement Effects)

To model the PD incidence over time, pneumococcal serotypes were typically summarized into groups according to the considered pneumococcal vaccines. Only the study by Thorrington et al. [32] included individual serotypes that are covered in PCV13 and not in PCV10 into the projection, with an assumption about the stable incidence for serotypes 3 and 6A and an indirect reduction in the incidence due to serotype 19A caused by the replacement of PCV10 with PCV13 in the childhood vaccination.

3.2.3.1 Indirect Effects of Childhood Vaccination with PCV13 on IPD Incidence Among the Elderly Out of the 13 included studies, 11 [8–10, 25–31, 33] evaluated pneumococcal vaccination of the elderly in the presence of a PCV13 program in children, which had replaced the PCV7 program.

We found different methods to project the epidemiological development of the serotype groups in the presence of routine childhood vaccination with PCV13. The Australian studies by Dirmesropian et al. [30] and Chen et al. [8, 9] started with an epidemiological steady state based on the national surveillance data and kept the future serotype-specific PD burden constant. Chen et al. [8] also looked into the potential changes in the PCV13-serotype epidemiology.

Other method to project indirect effects of PCV13 infant vaccination was to simulate an ongoing gradual decline of infections due to six additional (contained in PCV13 but not in PCV7) serotypes until elimination or near-elimination is reached, and include an increase of infections due to the non-PCV13 strains. In the Belgian studies, Blommaert et al. [26] and Willem et al. [10] applied an annual indirect reduction in PD incidence preventable by vaccination with PCV13 and did not report post-vaccination stabilization of the serotype distribution. Blommaert et al. [26] modeled the herd effect of the childhood PCV13 vaccination as an exponential decay with a 24% annual decrease in circulation of the PCV13-type serotypes and the vaccine-induced replacement effect was applied as a compensation of the reduction in incidence originating from the herd effect by 50% in the base case. The values were based on the observed PCV7-serotype circulation in Belgian children. Willem et al. [10] applied the indirect reduction of PD incidence in adults as an annual 16% decline of PCV13 serotypes in PCV13-serotype IPD incidence. Of this decline, 76.3% was compensated with occurrence of non-PCV13 serotypes in IPD incidence as the vaccine-induced serotype replacement. Stoecker et al. [28] and van Hoek and Miller [29] projected a decline of the six PCV13-minus-PCV7 serotypes, similar to the indirect reduction of PCV7 serotypes in IPD incidence in the elderly observed in the national epidemiological data, with a

post-vaccination stabilization during the modeled time horizon comparable to the remaining PCV7 PD disease burden.

Jiang et al. [24] estimated the PD incidence from the German surveillance data and modeled the indirect effects of a PCV13 program in children on the IPD incidence among adults to follow the PCV7 effects observed in the USA. The authors applied stabilization of serotypes in 2012, 7 years after the introduction of the PCV7 vaccination and only 2 years after the replacement of PCV7 with PCV13. The evaluated vaccination of the elderly started in 2011; therefore, the cost effectiveness was evaluated under the assumptions that IPD incidence had stabilized after 1 year since the start of the program in the elderly. Therefore, the projection applied by Jiang et al. [24] can be considered to resemble the steady-state scenarios in the Australian studies [8, 30].

Thorrington et al. [32] analyzed a scenario in which PCV13 replaced PCV10 in the infant vaccination. It was assumed that the low PCV7 PD incidence remained stable. The indirect effects of higher valent PCV immunization of infants were projected based on the (historical) observed herd and replacement effects of PCV7 childhood vaccination. Under the PCV10 childhood vaccination, the incidence of IPD caused by the three additional serotypes included in PCV10 among the elderly was projected to decline over 5 years while the incidence of PCV13-minus-PCV10 serotypes remained stable. PCV13 infant vaccination was assumed to have the same effects on PCV10 serotypes. Additionally, the impact of PCV13 on vaccine serotypes 3, 19A, and 6A was analyzed based on the post-PCV13 serotype epidemiology observed in other countries. Based on this data, the authors projected a 40% decrease in the 19A serotype and no impact of PCV13 on serotypes 3 and 6A. The IPD incidences caused by PPSV23-minus-PCV13 and non-vaccine serotypes were projected to increase with the same rate as the observed serotype replacement induced by PCV7 but over a longer period in case of a replacement of PCV10 by PCV13.

Three studies [27, 31, 33] applied an all-serotype approach (described in ESM file S1: section 1.2.2) to project the indirect effects in IPD among the elderly. This approach assumes a perfect correlation between all-serotype PD incidence and serotype-specific PD incidence (i.e., a 2% reduction in IPD of pneumococcal origin results in a 2% reduction of IPD caused by PCV13 serotypes).

3.2.3.2 Indirect Effects of Childhood Vaccination with PCV10 on IPD Incidence Among the Elderly

One study [25] assessed the cost effectiveness of PCV13 vaccination in the elderly in the presence of PCV10 infant vaccination, which had replaced the PCV7 program. Two studies [10, 32] analyzed the possible impact of changing one higher-valent PCV with another; that is, replacement of PCV10 with PCV13 [32] and replacement of PCV13 with PCV10 [10].

The study by Mangen et al. [25] was the only analysis that evaluated pneumococcal vaccination of the elderly in a scenario with PCV10 infant vaccination present, which had replaced PCV7 vaccination program. The study applied equilibrium of PCV13 serotypes assuming no indirect effects of PCV10 vaccination. In addition, no projections of serotypes 3, 6A, and 19A were made.

In an additional scenario, Willem et al. [10] analyzed the impact of replacing PCV13 with PCV10 infant vaccination on the cost effectiveness of pneumococcal vaccination in the elderly. For this scenario, a relapse of PCV13 serotype incidence within 7 or 15 years was assumed and modeled by applying a logistic curve.

3.2.3.3 Indirect Effects of PCV Childhood Vaccination on Non-bacteremic Pneumococcal Pneumonia (NBPP) Incidence Among the Elderly

Nine studies [8–10, 25, 26, 28–30, 32] assumed the same serotype-specific dynamics in NBPP incidence as for IPD. Jiang et al. [24] did not describe the effects of infant vaccination on NBPP in the elderly. We also identified three studies [27, 31, 33] that used all-cause and all-serotype approaches (described in ESM file S1: section 1.2.2) to project indirect effects on NBPP incidence among the elderly. The all-cause approach assumes a perfect correlation between percentage changes in all-cause non-bacteremic pneumonia (NBP) and serotype-specific NBPP (i.e., a 2% reduction in all-cause NBP results in a 2% reduction of PCV13-NBPP). Both approaches are not valid and misrepresent possible real evolution of the serotype-specific PD incidences as described in the ESM in detail (file S1: section 1.2.2).

3.2.4 Selection of Studies for Reporting the Cost Effectiveness

The selected studies were evaluated on 11 dimensions of economic evaluation for consistency in reporting and relevance to decision making, and the scores were classified as low (≤ 2), middle (3), and high (4) (see Table 2). A short summary and the complete assessment of the quality of the economic evaluation can be found in the ESM (file S5). For the studies by Jiang et al. [24], Rodriguez Gonzalez-Moro et al. [27], Heo et al. [31], and Kuchenbecker et al. [33] we found weaknesses in the reporting and in the applied methods of modeling the VE and the indirect effects and hence considered them of low validity for decision making. These studies were excluded from the reporting of the cost-effectiveness estimates in this review.

In the Korean study by Heo et al. [31], the main limitations were seen using the all-serotype approach in the modeling of the indirect effects of the childhood vaccination, which may have led to the contrastingly low ICER estimates. Weaknesses were also found for other dimensions of the

Table 2 Overview of the methods used to predict vaccine effects ($n = 13$)

Study, EVIDEM score	PCV13			PPSV23		
	Source (CAPiTA) [7]	Age adjustment	Risk-group adjustment	Source	Age adjustment	Risk-group adjustment
Initial vaccine efficacy against vaccine serotypes						
Jiang et al., 2012 Germany [24] 3/2	n/a	n/a	n/a	VT-IPD: Cochrane Review 2008 [47], IPD VE VT-NBPP: EVAN study [48]	No	VT-IPD: Rodriguez-Barradas et al. 2008 [49] VT-NBPP: No protection; assumption
Mangen et al., 2015 Netherlands [25] 4/3	VT-IPD: VT-IPD PP VT-NBPP: VT-NBPP PP	Age-specific: 3.7% per year [50, 51] extrapolated to the VE against VT-IPD or VT-NBPP relative to VT-PnP; for > 85 y.o. VE is fixed on the level of 85 y.o.	Immunosuppressed: VT-IPD: VE 22% lower [52] VT-NBPP: VE 35% lower [52]	n/a	n/a	n/a
Blommaert et al., 2016 Belgium [26] 4/4	VT-IPD: VT-IPD PP VT-NBPP: VT-NBPP mITT	No	n/a	VT-IPD: Cochrane Review 2013 [53] lower 95% CI of IPD VE VT-NBPP: No protection; assumption	No	n/a
Rodriguez Gonzalez-Moro et al., 2016 Spain [27] 3/2	VT-IPD: analysis not stated VT-NBPP: analysis not stated	Age-group-specific: Adjustment methods not described	n/a	VT-IPD: Andrews et al. 2012 [15] VT-NBPP: No protection; Cochrane Review 2013 [53]	Age-group-specific: Adjustment methods not described	n/a
Stoecker et al., 2016 USA [28] 3/3	VT-IPD: VT-IPD PP VT-NBPP: VT-NBPP PP	No	n/a	VT-IPD: Cochrane Review 2008 [47] VT-NBPP: No protection; Huss et al. 2009 [54]	No	n/a
van Hoek and Miller, 2016 England [29] 2/3	VT-IPD: VT-IPD PP VT-NBPP: VT-NBPP PP	No	n/a	n/a	n/a	n/a
Dirmesropian et al., 2017 Australia [30] 3/3	VT-IPD: VT-IPD mITT VT-NBPP: VT-NBPP mITT	Age-specific: VT-IPD: 7.8% per year [50] VT-NBPP: 5.0% per year [50]	n/a	VT-IPD: Andrews et al. 2012 [15] VT-NBPP: no protection; assumption	Age-specific: VT-IPD: fixed for < 75 y.o.; logistic function for 75+ y.o.[a]	n/a

Table 2 (continued)

Study, EVIDEM score	PCV13			PPSV23		
	Source (CAPiTA) [7]	Age adjustment	Risk-group adjustment	Source	Age adjustment	Risk-group adjustment
Heo et al., 2017 Korea [31] 3/2	VT-IPD: VT-IPD PP VT-NBPP: VT-NBPP PP	Age-group-specific: adjusted in proportion to VE in Smith et al. 2012 [40]	Chronic conditions VT-IPD: VE 15% lower [52] VT-NBPP: VE 20% lower [52] Immunosuppressed: VT-IPD: VE 22% lower [52] VT-NBPP: VE 35% lower [52]	VT-IPD: Cochrane Review 2013 [53], VE against VT-IPD VT-NBPP: no protection; various studies [40, 50, 53]	Age-group-specific: VT-IPD: adjusted in proportion to VE in Smith et al. 2012 [40]	VT-IPD: VE 20% lower in patients with chronic conditions and VE base 20% in immunosuppressed [47, 55]
Chen et al., 2018 Australia [8, 9] 3/3; 3/4	VT-IPD: VT-IPD mITT VT-NBPP: VT-NBPP mITT	Age-specific: VT-IPD: 7.8% per year [50] VT-NBPP: 5.0% per year [50]	n/a	n/a	n/a	n/a
Thorrington et al., 2018 Netherlands [32] 3/3	VT-IPD: VT-IPD PP VT-NBPP: VT-PnP mITT	No	n/a	VT-IPD: Falkenhorst et al. 2017 [56] VT-NBPP: Assumption[b]	No	n/a
Willem et al., 2018 Belgium [10] 4/4	VT-IPD: VT-IPD mITT VT-NBPP: VT-NBPP mITT	Age-specific: VT-IPD: 5.8% per year [50] VT-NBPP: 5.8% per year [50]	n/a	VT-IPD: Andrews et al. 2012 [15] VT-NBPP: VT-IPD VE multiplied by ratio of VT-NBPP VE to VT-IPD VE in Ochoa-Gondar et al. [57]	No (but no effectiveness in 85+ y.o.)	n/a
Kuchenbecker et al., 2018 Germany [33] 2/2	VT-IPD: VT-IPD PP VT-NBPP: VT-NBPP PP	Age-specific: 50% of PPSV23 age effects	Immunosuppressed: VT-IPD: VE 22% lower [52] VT-NBPP: VE 35% lower [52]	VT-IPD: Shapiro et al. 1991 [58], Smith et al. 2008 [61] VT-NBPP: no protection; various studies [53, 59, 60]	Age-specific: VT-IPD: linear interpolation of VE values assumed by Smith et al. 2008 [61]	Immunosuppressed: VT-IPD: Shapiro et al. 1991 [58], Fry et al. 2002 [62][c]

Table 2 (continued)

Study	PCV13	PPSV23
Waning of vaccine protection		
Jiang et al., 2012 Germany [24]	n/a	Annual decline of VE to 0% at 9 years since vaccination Waning increases with time since vaccination
Mangen et al., 2015 Netherlands [25]	No waning of VE during the first 5 years since vaccination, afterwards VE wanes annually at a rate of 5% during 6–10 years since vaccination, 10% annually during 11–15 years since vaccination and drops to 0% VE after 15 years since vaccination	n/a
Blommaert et al., 2016 Belgium [26]	No waning of VE during the first 5 years since vaccination, followed by an instant drop to 0% VE	No waning of VE during the first 5 years since vaccination, followed by an instant drop to 0% VE
Rodriguez Gonzalez-Moro et al., 2016 Spain [27]	Stepwise decline of VE over time since vaccination Waning depends on age and time since vaccination Waning stops (stable VE) after year 15 since vaccination when vaccination age < 85 years VE drops to 0% in year 11 since vaccination when vaccination age is ≥ 85	Stepwise decline of VE over time since vaccination Waning depends on age and time since vaccination Waning stops (stable VE) after year 15 since vaccination when vaccination age < 75 years VE drops to 0% in year 16 since vaccination when vaccination age is ≥ 75 years and < 85 years VE drops to 0% in year 6 since vaccination when vaccination age is ≥ 75 years and < 85 years
Stoecker et al., 2016 USA [28]	No waning of VE in individuals aged < 65 years until they reach the age of 65 years In 65+ y.o., VE wanes by 10% every 5 years, with waning distributed linearly within each 5-years increment	Stepwise linear decline of the initial VE: from 100% to 50% over the first 5 years since vaccination, from 50% to 30% in years 5–10 since vaccination and 30% to 0% in years 10–15 since vaccination
van Hoek and Miller, 2016 England [29]	Stepwise decline of VE over time: 100% of initial VE in years 1–9 after vaccination, 57% of initial VE in years 10–14, 12% of initial VE in years 15–19, 7% of initial VE in years 20+	n/a
Dirmesropian et al., 2017 Australia [30]	No waning of VE in the first 5 years since vaccination, followed by a linear decline to 0% VE over the next 5 years	No waning of VE during the first 2 years since vaccination, followed by a linear decline to 0% VE over the next 3 years
Heo et al., 2017 Korea [31]	Stepwise decline of VE over time since vaccination Waning depends on age and time since vaccination Waning stops (stable VE) after year 15 since vaccination when vaccination age < 75 years VE drops to 0% in year 10 since vaccination when vaccination age is ≥ 75 years	Stepwise decline of VE over time since vaccination Waning depends on age and time since vaccination VE drops to 0% in year 15 since vaccination when vaccination age is < 65 years VE drops to 0% in year 10 since vaccination when vaccination age is ≥ 65 years
Chen et al., 2018 Australia [8, 9]	No waning of VE in the first 5 years since vaccination, followed by a linear decline to 0% VE over the next 6 years	n/a
Thorrington et al., 2018 Netherlands [32]	No waning of VE during the first 4 years since vaccination, then VE wanes linearly to 0% by year 15 after vaccination	VE wanes linearly to 0% by year 10 after vaccination
Willem et al., 2018 Belgium [10]	No waning of VE during the first 5 years since vaccination, then logistic waning with a half-life of 5 years (i.e., VE is reduced to 50% of initial VE at 10 years since vaccination) and a waning rate of 0.75	No waning of VE during the first 2 years since vaccination, then exponential waning with a half-life of 1.5 (i.e., VE is reduced to 50% of initial VE at 3.5 years since vaccination)

Table 2 (continued)

Study	PCV13	PPSV23
Kuchenbecker et al., 2018 Germany [33]	No waning of VE during the first 5 years after waning, then VE declines at the rate of 50% of the rate for PPSV23 (i.e., reduction of PCV13 VE in the 6th year since vaccination equal to 50% of the reduction of PPSV23 VE in the first year since vaccination and so on) VE drops to 0% in year 16 since vaccination	VE estimates of Smith et al. 2008 [61] are applied Smith et al. 2008 [61] report VE for specific ages and years since vaccination. These values are linearly interpolated by Kuchenbecker et al. 2018 [33] VE drops to 0% in year 16 since vaccination

Study	Infant vaccination	Indirect effects in IPD		Indirect effects in NBPP
		Indirect herd effects	Replacement effects	
Indirect effects of childhood vaccination				
Jiang et al., 2012 Germany [24]	PCV13	Changes in IPD incidence are modeled as gamma functions of cumulative vaccine uptake in children; the parameters are estimated based on the USA post-PCV7 data. Additional serotypes in PCV13 are assumed to follow the same pattern as PCV7 serotypes. Coverage rates observed in German children are applied to obtain the IPD incidence. Stable incidence is assumed after 2012 (3 years after the start of PCV13 vaccination of infants in Germany)	Same methods as for indirect herd effects	Not described, probably not applied
Mangen et al., 2015 Netherlands [25]	PCV10	Stable PCV13-type IPD incidence is assumed in adults based on Dutch epidemiologic data [63]. Mangen et al. argue that either PCV10 infant vaccination does not cause further indirect herd effects or that additional serotypes in PCV13 will completely replace a reduction in PCV10 serotypes. Different indirect herd effect scenarios considered in the sensitivity analyses	Assumption: No replacement effects if PCV10 does not cause further indirect herd effects or that additional serotypes in PCV13 will completely replace a reduction in PCV10 serotypes. Replacement disease by non-PCV13 serotypes not relevant to the study	Assumption: Same disease dynamics as projected for IPD
Blommaert et al., 2016 Belgium [26]	PCV13	In the absence of Belgian studies on herd effects in adults at the time of the study, indirect herd effects are estimated based on the effects of PCV7 infant vaccination among children aged 2–4 years in Belgium. An exponential decline with 24% yearly decrease of VE was applied for PCV7 serotypes and for the additional serotypes in PCV13 (sensitivity analyses 0%, 12%)	Non-PCV13 serotypes compensate for the reduction in the PCV13 incidence by 50% (sensitivity analysis 0%, 100%)	Assumption: Same disease dynamics as projected for IPD

Table 2 (continued)

Study	Infant vaccination	Indirect effects in IPD		Indirect effects in NBPP
		Indirect herd effects	Replacement effects	
Rodriguez Gonzalez-Moro et al., 2016 Spain [27]	PCV13	Indirect herd effects are defined as reductions in the overall IPD incidence. The maximum herd effect is assumed to be reached in the fifth year after the introduction of PCV13 infant vaccination, which seems to coincide with the start of the modeling time horizon. Applied values differ from data reported in the cited US studies and further description of the methods is not provided	Not applied	Indirect herd effects are defined as reductions in the overall NBP incidence. Methodological approach is comparable to the modeling of indirect effects in IPD. Applied values differ from data reported in the cited US studies and further description of the methods is not provided
Stoecker et al., 2016 USA [28]	PCV13	The decline of PCV7-type IPD incidence between 2003 and 2009 was projected onto IPD of additional serotypes in PCV13 for 2013–2019: 78.6% for 50–64 y.o. and 86.6% for ≥ 65 y.o. The calculations are based on the national surveillance data	Estimated increase of PPSV23–PCV13 serotypes in 2003–2009: 77.9% for 50–64 y.o. and 17% for ≥ 65 y.o. This increase is applied to IPD incidence (of 2013) for PPSV23–PCV13 serotypes starting in 2019. IPD incidence is scaled for the serotype groups (PCV13–PCV7, PPSV23–PCV13, NVT) linearly between years 0 and 6. Stabilization after year 6 is assumed	Assumption: Same disease dynamics as projected for IPD
van Hoek and Miller, 2016 England [29]	PCV13	Indirect herd effects were calculated based on the serotype-specific UK surveillance data (epidemiological years July to June from 2002/2003 to 2013/2014). For the projection of the future PCV13 disease incidence, the following assumptions were made: (i) PCV7 types reached a new post-vaccination equilibrium in season 2013/2014; (ii) the additional six types covered by PCV13 will experience a similar reduction in IPD as the PCV7 types, with a similar post-vaccination steady state in season 2018/2019	Not relevant to the study	Assumption: Same disease dynamics as projected for IPD
Dirmesropian et al., 2017 Australia [30]	PCV13	Based on the epidemiological data from the NNDSS (Australian Department of Health and Ageing), it is assumed that a stable post-PCV13 infant vaccination plateau is reached in 2015. Hence, age- and serotype-specific PCV13-IPD incidence remained constant over the modeled time horizon	Stable post-PCV13 infant vaccination plateau is reached at the start of the modeled time horizon. Hence, replacement effects are not applied	Assumption: Same disease dynamics as projected for IPD

Table 2 (continued)

Study	Infant vaccination	Indirect effects in IPD		Indirect effects in NBPP
		Indirect herd effects	Replacement effects	
Heo et al., 2017 Korea [31]	PCV13	Indirect herd effects are defined as reductions in the overall IPD incidence. Assumed age-group-specific herd effects in 2014 are based on post-PCV13 US data and are assumed to reach a maximal steady level in 2018 according to post-PCV7 US data	Not applied	Indirect herd effects are defined as reductions in the overall NBPP incidence and are assumed to be 50% of herd effects in IPD
Chen et al., 2018 Australia [9]	PCV13	Based on the epidemiological data from the NNDSS (Australian Department of Health and Ageing), it is assumed that a stable post-PCV13 infant vaccination plateau is reached in 2015. Hence, age- and serotype-specific PCV13-IPD incidence remained constant over the modeled time horizon	Not relevant to the study	Assumption: Same disease dynamics as projected for IPD
Chen et al., 2018 Australia [8]	PCV13	Two scenarios: (i) Based on the epidemiological data from the NNDSS (Australian Department of Health and Ageing), it is assumed that a stable post-PCV13 infant vaccination plateau is reached in 2015. Hence, age- and serotype-specific PCV13-IPD incidence remained constant over the modeled time horizon (ii) Sex additional PCV13 serotypes decline from 2016 as observed in PCV7 serotypes	Not relevant to the study	Assumption: Same disease dynamics as projected for IPD

Table 2 (continued)

Study	Infant vaccination	Indirect effects in IPD		Indirect effects in NBPP
		Indirect herd effects	Replacement effects	
Thorrington et al., 2018 Netherlands [32]	PCV10 to PCV13	The following assumptions are applied for the projection of the future PCV13-type incidence: PCV7 serotypes IPD incidence remains stable (data based) PCV10–PCV7 serotype IPD incidence declines over 5 years till the impact of PCV7 is reached then drops to 0.8/100,000 -PCV13–PCV10 serotype IPD: if infant vaccination is with PCV10—stable; if PCV13—declines but less than PCV7 and PCV10 serotypes Three projections are evaluated: PCV10 infant vaccination with herd effects for PCV10–PCV7 PCV13 among infants with herd immunity against serotype 19A among ≥60 y.o.: 40% and 90%	PPSV23–PCV13 and non-PPSV23 serotypes increase due to replacement, based on observed data for PPSV23–PSV7. The overall IPD incidence linearly increases (by estimated linear trend of PPSV23 and non-PPSV23 serotypes) to the pre-PCV level of 2005/06 of 54/100,000 among ≥60 y.o.	Assumption: same disease dynamics as projected for IPD
Willem et al., 2018 Belgium [10]	PCV13 to PCV10	Several scenarios: Base case: PCV13 serotype incidence declines by 16% per year (average of SPIDNET of changes of non-PCV7 PCV13 serotypes) Minimum scenario: PCV13 serotype incidence declines by 10% per year (rounded minimum yearly decline SPIDNET data of changes of non-PCV7 PCV13 serotypes) Maximum scenario: PCV13 serotype incidence declines by 20% per year (rounded maximum yearly decline SPIDNET data of changes of non-PCV7 PCV13 serotypes) Quick relapse: PCV13 serotype incidence declines by 16% per year before it returns to its 2015 value within 7 years (logistic curve applied) Slow relapse: PCV13 serotype incidence declines by 16% per year before it returns to its 2015 value within 15 years (logistic curve applied)	Several scenarios: Base case, minimum, maximum scenario: non-PCV13 serotype incidence increases by 76.3% of the reduction of the PCV13 serotype incidence per year Quick relapse, slow relapse: stable non-PCV13 serotype incidence	Assumption: same disease dynamics as projected for IPD

Table 2 (continued)

Study	Infant vaccination	Indirect effects in IPD		Indirect effects in NBPP
		Indirect herd effects	Replacement effects	
Kuchenbecker et al., 2018 Germany [33]	PCV13	Indirect herd effects are defined as reductions in the overall IPD incidence Cumulative herd effects are expressed in % for each age group over the first 5 years of the modeling time horizon before the maximum steady effect is reached in the 5th year. The reported % show that the cumulative herd effects reach over 80% of the maximum effects by year 2 in all age groups but 75–99 y.o. These cumulative herd effects are derived from projections of the PCV13-type IPD proportion but methods for the calculation of dynamics in IPD incidences based on dynamics in serotype distributions are not reported. Age-group-specific PCV13-serotype IPD proportions are projected by applying regression non-linear models of the best fit, which are estimated using observed serotype-specific IPD data (unpublished) over the past 5 years	Not applied	Indirect herd effects are defined as reductions in the overall NBP incidence. The reduction in the NBP incidence is obtained from published serotype distribution in NBPP [64]. Methods for the calculation of dynamics in NBP incidences based on dynamics in NBPP serotype distributions are not reported. Replacement effects are not applied

95% CI 95% confidence interval, *EVIDEM* Evidence and Value: Impact on DEcisionMaking tool, *IPD* invasive pneumococcal disease, *n/a* not applicable, *NBPP* non-bacteremic pneumococcal pneumonia, *NVT* non-vaccine types, *PnP* pneumococcal pneumonia, *PP* per protocol, *mITT* modified intention to treat, *NNDSS* National Notifiable Diseases Surveillance Scheme, *SPIDNET* Streptococcus Pneumoniae Invasive Disease Network, *VE* vaccine efficacy, *VT* vaccine-type, *y.o.* years old

[a]Logistic function 0.58/(1 + 2.2898^(age − 85.5)) was estimated based on data from Andrews et al. 2012 [15]

[b]Assumptions: (i) PPSV23 has the same effectiveness against pneumonia as PCV13 (CAPiTA [7] mITT) at the time of vaccination; (ii) 30% of pneumonia episodes are caused by *S. pneumoniae*. Based on these assumptions and observed serotype distributions in pneumococcal pneumonia in the Netherlands, the VT-NBPP VE of PPSV23 was calculated

[c]VE VT-IPD in immunosuppressed: 50 y.o. 21% (16), 69 y.o. 0% (19), linear interpolation between both ages. Waning proportional to immunocompetent patients

Table 3 Study design and cost-effectiveness results of the studies selected for reporting the cost-effectiveness estimates ($n = 9$)

Author, year, Country, funding	Model, time horizon	Perspective; costs included, reference year	Vaccine price, US PPP, 2007	Discount (cost, outcome)	Vaccination strategy, uptake rate	ICER (in $US PPP per QALY)				WTP stated and converted to $US PPP per QALY	Conclusion of the study
						PPSV23 vs NV	PCV13 vs NV	PCV13 vs PPSV23	PCV13 + PPSV23 vs PPSV23		
Childhood vaccination with PCV13: ongoing indirect effects											
Blommaert et al., 2016, Belgium [26], assumed basic academic funds	Static multi-cohort model, lifetime	Healthcare payer's; VC, age-specific hospitalization costs, medical costs per out-PP, cost of PMS, 2014	PCV13: US$100 PPSV23: US$38	3%, 1.5%	age groups: 50–64 y.o.; 64–74 y.o.; ≥75 y.o., 75%	50–64 y.o.: 169,584 65–74 y.o.: 88,415 ≥75 y.o.: 65,486	50–64 y.o.: 287,917 65–74 y.o.: 131,104 ≥75 y.o.: 88,842	Not considered	Estimate is not stated but concluded to be highly unlikely to be cost effective	€35,000 $46,062	Vaccination with PCV13 is unlikely to be cost effective in Belgium. The difference in the cost effectiveness between vaccinations with PCV13 and PPSV23 is caused by the large vaccine price difference
Stoecker et al., 2016, USA [28], CDC	Monte Carlo simulation, single cohort, lifetime	Societal; VC, inpatient and outpatient costs, 2013	PCV13: US$97	3%, 3%	Add PCV13 or replace PPSV23 at ages 50, 60, or 65 y.o., 27.2–61.4%	Not considered	Not considered	At age 65 y.o. 50,891	At age: 50 y.o.: 365,482 60 y.o.: 261,307 65 y.o.: 68,078	Not reported	Addition of one dose of PCV13 to the vaccination with PPSV23 and replacement of PPSV23 with PCV13 at 65 y.o. are cost-effective strategies. Herd effects of the pediatric vaccination strongly influence the cost-effectiveness estimate of PCV13

Table 3 (continued)

Author, year, Country, funding	Model, time horizon	Perspective; costs included, reference year	Vaccine price, US PPP, 2007	Discount (cost, outcome)	Vaccination strategy, uptake rate	ICER (in $US PPP per QALY)				WTP stated and converted to $US PPP per QALY	Conclusion of the study
						PPSV23 vs NV	PCV13 vs NV	PCV13 vs PPSV23	PCV13 + PPSV23 vs PPSV23		
van Hoek and Miller, 2016, England [29], NIHR HPRU	Static single cohort, lifetime	Healthcare payer's; VC, DHC for IPD, in-CAP, 2014	PCV13: US$73	3%, 3%	≥ 65 y.o., 69%	Not considered	Not considered	Not considered	375,622	£20,000 $29,144	PCV13 + PPSV23 can be efficacious but is unlikely to be cost effective. The optimal age of vaccination is suggested to be 75 years. The effects of the pediatric vaccination with PCV13 on the incidence among the elderly make the elderly vaccination with PCV13 not cost effective
Chen et al., 2018, Australia [8], assumed basic academic funds	Markov multi-cohort, 10 years + lifetime follow-up	Healthcare system, VC, inpatient costs for IPD and CAP and outpatient costs for CAP, 2016	PCV13: US$47	5%, 5%	≥ 65 y.o.	Not considered	Serotype steady state of 2016: 50,359 Evolution: 121,288	Not considered	Not considered	A$60,000 $42,557	Serotype changes caused by the infant PCV13 programs are critical to the cost effectiveness of adult PCV13 programs

Table 3 (continued)

Author, year, Country, funding	Model, time horizon	Perspective; costs included, reference year	Vaccine price, US PPP, 2007	Discount (cost, outcome)	Vaccination strategy, uptake rate	ICER (in $US PPP per QALY)				WTP stated and converted to $US PPP per QALY	Conclusion of the study
						PPSV23 vs NV	PCV13 vs NV	PCV13 vs PPSV23	PCV13 + PPSV23 vs PPSV23		
Willem et al., 2018, Belgium [10], Belgian Health Care Knowledge Centre, a Belgian government agency	Static multicohort, lifetime	Healthcare payer's; DHC as per-event total costs, no prices, resources framework is used, 2015	PCV13: US$97 PPSV23: US$37	3%, 1.5%	Age groups: 50–64 y.o.; 65–74 y.o.; 75–84 y.o., Combination at different uptake levels	50–64 y.o.:[a]107,282 65–74 y.o.: 74,116 75–84 y.o.: 67,554	Not considered	50–64 y.o.: 260,611 65–74 y.o.: 221,970 75–84 y.o.: 438,072	50–64 y.o.: 218,776 65–74 y.o.: 171,765 75–84 y.o.: 201,308	€50,000 $64,773 Analyze ranges of WTP up to €350,000 $453,411	PPSV23 + PCV13 is most effective but less cost effective. Vaccination would be most cost effective if high uptake with PPSV23 in 75–84 y.o. and a lower PPSV23 price. For < 75 y.o., PCV13 could become attractive when duration of PCV13 protection and disease burden preventable by PCV13 increase and PCV13 price is reduced by 75%. For ≥ 75 y.o., PPSV23 is more attractive. The current strategy of PPSV23 is cost effective

Table 3 (continued)

Author, year, Country, funding	Model, time horizon	Perspective; costs included, reference year	Vaccine price, US PPP, 2007	Discount (cost, outcome)	Vaccination strategy, uptake rate	ICER (in $US PPP per QALY)				WTP stated and converted to $US PPP per QALY	Conclusion of the study
						PPSV23 vs NV	PCV13 vs NV	PCV13 vs PPSV23	PCV13 + PPSV23 vs PPSV23		
Childhood vaccination with PCV13: serotypes reached stability											
Dirmesropian et al., 2017, Australia [30], Australian National Health and Medical Research Council Project grant	Markov, single cohort, lifetime	Healthcare system; VC, aggregated DHC, 2016	PCV13: US$47 PPSV23: US$25	5%, 5%	At 65 y.o. and different ages of vaccine administration, 60%	210,800	62,417	25,038	Not considered	A$60,000 $42,557	PCV13 and PPSV23 are not cost effective compared with a no-vaccination strategy Vaccination of 65 y.o. with PCV13 is cost effective vs current PPSV23 vaccination
Chen et al., 2018, Australia [9], assumed basic academic funds	Markov multicohort, 10 years + lifetime follow-up	Healthcare system; VC, inpatient costs for IPD and CAP and outpatient costs for CAP, 2016	PCV13: US$47	5%, 5%	≥65 y.o. Two uptake strategies: Observed and recommended: total cumulative uptake	Not considered	59,252 for recommended age 46,294 for observed age	Not considered	Not considered	A$60,000 $42,557	The timeliness of vaccination plays an important role and should be considered for vaccination recommendations
Childhood vaccination with PCV10: hypothetical scenarios of vaccine replacement with consequent ongoing indirect effects											
Thorrington et al., 2018, Netherlands [32], European Council grant and NIHR HPRU	Static cost-effectiveness model, single cohort for 5 age cohorts, 10 years	Healthcare provider's; DHC per IPD and CAP, no further detail, year is not stated	PCV13: US$95 PPSV23: US$28	4%, 1.5%	≥65 y.o., 50% + replacement PCV10 with PCV10 in infants	vs PCV10 for infants and PPSV23 for HR groups: at 60 y.o.: 18,469 at 70 y.o.: 7925	Not considered	vs PCV10 for infants and PPSV23 for HR groups: at 60 y.o.: 85,364	Not considered	€20,000 $25,560	PPSV23 single-dose vaccination of elderly aged 60–70 years is the most cost-effective strategy

Table 3 (continued)

Author, year, Country, funding	Model, time horizon	Perspective; costs included, reference year	Vaccine price, US PPP, 2007	Discount (cost, outcome)	Vaccination strategy, uptake rate	ICER (in $US PPP per QALY)				WTP stated and converted to $US PPP per QALY	Conclusion of the study
						PPSV23 vs NV	PCV13 vs NV	PCV13 vs PPSV23	PCV13 + PPSV23 vs PPSV23		
Willem et al., 2018, Belgium [10], Belgian Health Care Knowledge Centre, a Belgian government agency	Static multicohort, lifetime	Healthcare payer's; DHC as per-event total costs, no prices, resources framework is used, 2015	PCV13: US$97 PPSV23: US$37	3%, 1.5%	Age groups: 50–64 y.o.; 65–74 y.o; 75–84 y.o.	Not stated	Not stated	Not stated	Not stated	€50,000 $64,773; ranges of WTP up to €350,000	Quick serotype relapse: PPSV23 with revaccination of 50–84 y.o. is the most beneficial strategy from WTP of €50,000–€130,000 Slow serotype relapse: PCV13 + PPV23 with revaccination in the age group 50–74 years is beneficial from WTP of €175,000
Childhood vaccination with PCV10: serotypes reached stability											
Mangen et al., 2015, Netherlands [25], Pfizer Inc.	Probabilistic Markov-type model, lifetime	Societal; VC, DHC and INHC per IPD, in-, out-CAP, DNHC, 2012	PCV13: US$108	4%, 1.5%	12 strategies, variation of age range of eligibility and the group of pneumococcal disease risk, 63.9%: LR 81.5%: MR/HR	Not considered	65–74 y.o. 12,003	Not considered	Not considered	GDP: €35,300 $65,329 Cost effective if ICER ≤$105,900/QALY	All strategies of PCV13 (except PCV13 vaccination of only low-risk patients aged 65–74 years) are considered to be highly cost effective

CDC the Centers for Disease Control and Prevention, *CV* current vaccination policy at the time of the study, *DHC* direct healthcare costs, *DNHC* direct non-healthcare cost, *GDP* gross domestic product per capita, *HR* high risk, *ICER* incremental cost-effectiveness ratio, *in-CAP* inpatient community-acquired pneumococcal pneumonia, *INHC* indirect non-healthcare costs, *IPD* invasive pneumococcal disease, *LR* low risk, *MR* medium risk, *NIHR HPRU* the National Institute for Health Research Health Protection Research Unit in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England, *NV* no vaccination, *out-CAP* outpatient community-acquired pneumococcal pneumonia, *out-PP* outpatient pneumococcal pneumonia, *PMS* pneumococcal meningitis sequelae, *PPP* purchasing power parity, *QALY* quality-adjusted life-year, *VC* vaccine costs, *WTP* willingness-to-pay, *y.o.* years old

[a]Mean ICER of higher uptake of PPSV23 vs current vaccination with PPSV23 with low uptake

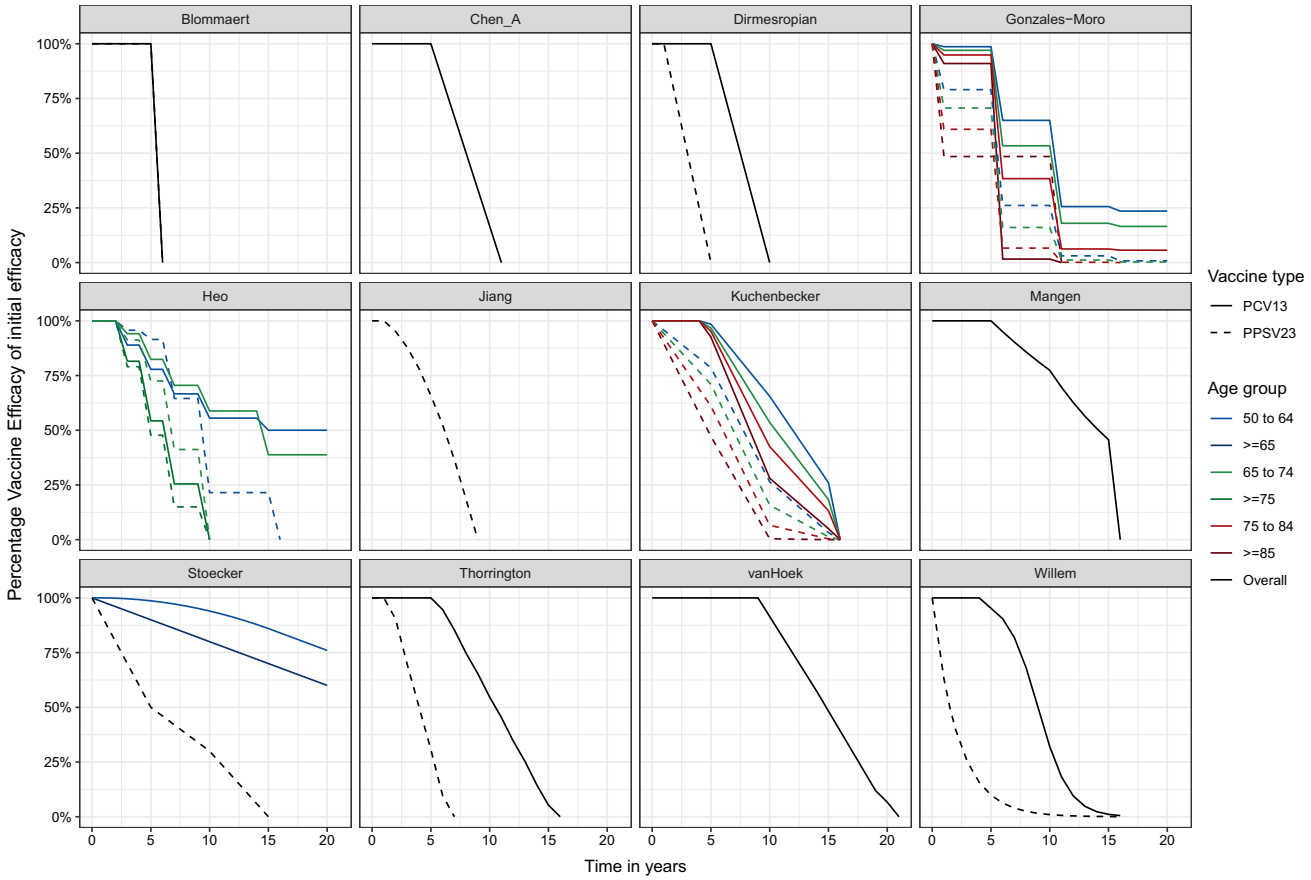

Fig. 3 Representation of constructed waning patterns reported in the selected studies by the first author, vaccine and age group (when reported). For the study by Stoecker et al. [28], for the age group 50–64 years, the plot represents the unweighted average curve due to the assumption of no waning for adults aged 50–64 years, and each single age cohort from 50 to 64 years had a different length of time with stable vaccine protection. The graph for Blommaert et al. [26] illustrates the assumption of the same waning pattern for both PCV13 and PPSV23

economic evaluation such as calculation of the indirect costs, time horizon, discounting, and sensitivity analysis (SA). In the Spanish study by Rodriguez Gonzalez-Moro et al. [27], vaccination with PCV13 of adults with chronic obstructive pulmonary disease (COPD) aged 50 years was evaluated, however, the φ with the population of the CAPiTA trial [7], which was used for definition of PCV13 VE. The authors applied a reduction in all-cause NBP incidence when modeling the herd effect of PCV13 childhood vaccination in NBPP. The all-cause approach was also used in modeling PCV13 VE against NBPP. The same methodological choices in modeling the vaccine effects in NBPP were seen in a recent German study by Kuchenbecker et al. [33]. The authors applied PCV13 VE of 3.9% against all-cause NBP and, in addition, used a longer duration of PCV13 and PPSV23 protection demonstrating high values of EVPOT. The herd effect for all-cause NBP was calculated based on the data from the study by Pletz et al. [64], who reported serotype distributions in NBPP. Kuchenbecker et al. [33] used the data on the serotype distributions for the calculation of the herd effect for both IPD and NBPP incidence, however, the authors did not report the methods for translation of the serotype distribution into the incidence of PD. We also excluded the German study by Jiang et al. [24] because of their assumption about the rapid stabilization of the vaccine-type serotypes in the PD incidence among the elderly in 2012 and absence of the indirect effects on NBPP incidence among the elderly.

3.2.5 Funding Source

Nine [8–10, 26, 28–32] of the 13 included studies reported industry-independent funding sources and the other four [24, 25, 27, 33] were funded by the industry. Three [24, 27, 33] of the industry-funded evaluations and one [31] of the studies with industry-independent funding were considered of

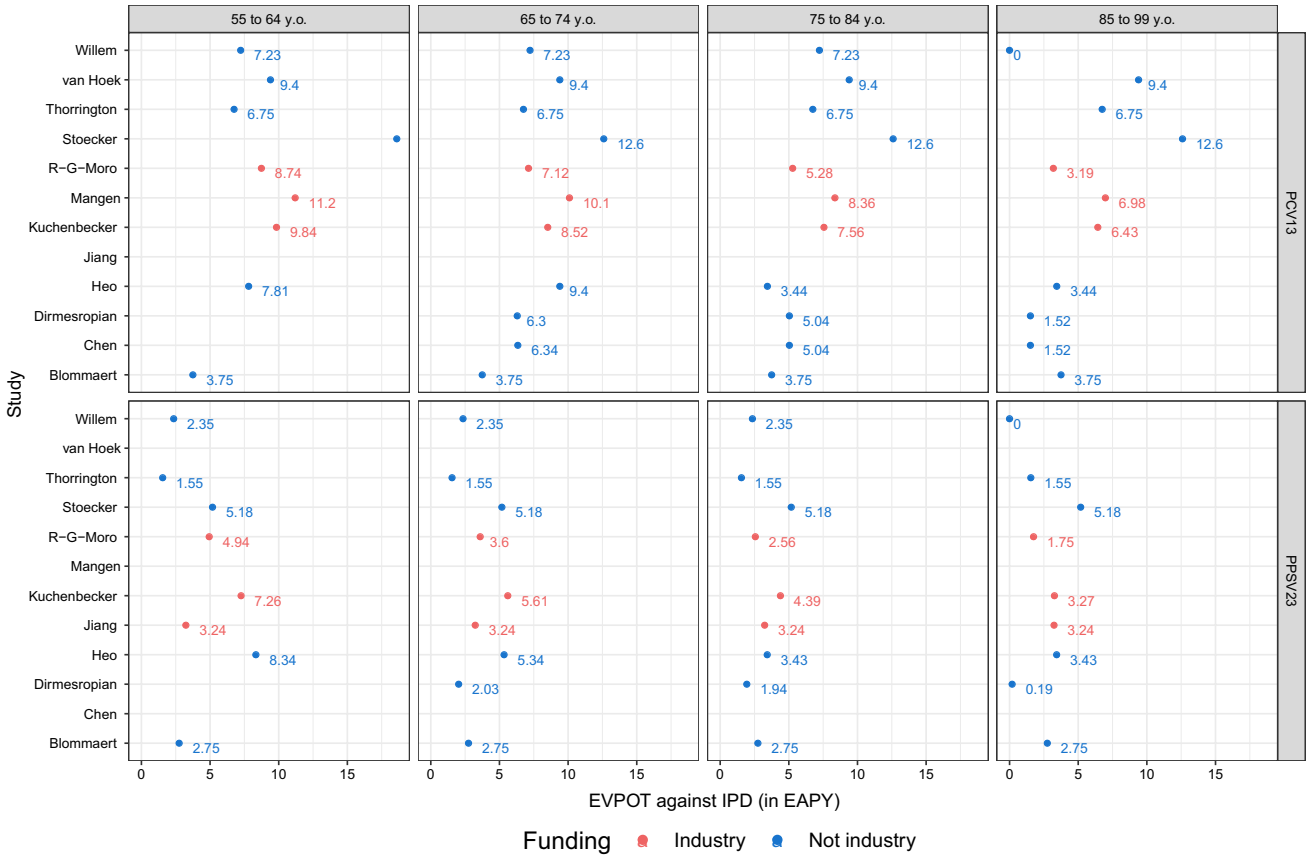

Fig. 4 Dot plot of the calculated expected vaccine protection over time (for details about the methods for the calculation see electronic supplementary material [ESM] file S1: section 1). *EAPY* efficacy-adjusted protection years, *EVPOT* expected vaccine protection over time, *IPD* invasive pneumococcal diseases, *y.o.* years old

low validity for the decision-making because of the flaws in modeling the indirect effects of the childhood vaccination. These studies are likely to underestimate the indirect PD reduction due to the PCV13 program in children. The assumptions about the duration of the vaccine protection seem to vary among the studies irrespectively of the funding source (see Fig. 4).

3.3 Cost Effectiveness of the Elderly Pneumococcal Vaccination in the Presence of a Routine Childhood Pneumococcal Conjugate Vaccination

In order to facilitate a comparative analysis of the findings on cost effectiveness of the adult vaccination, we included nine studies [8–10, 25, 26, 28–30, 32] that were considered relevant for decision making. We summarize the results by grouping the studies according to the vaccine used for the childhood vaccination and its effects on the PD incidence among the elderly. The results are summarized accordingly in Table 3. All reported prices and ICERs in this section are converted to 2017 US dollars (see ESM file S6 for the original and converted values of ICERs).

3.3.1 Childhood Vaccination with PCV13

3.3.1.1 Ongoing Indirect Effects Five [8, 10, 26, 28, 29] studies projected a future decline of PCV13 preventable PD incidence among the adult population due to the herd effect of the childhood vaccination with PCV13.

Adult vaccination with PPSV23 compared with no vaccination In the presence of ongoing effects of the childhood vaccination with PCV13, only the study by Blommaert et al. [26] reported the cost effectiveness of vaccinating the elderly with PPSV23 compared with no vaccination program. The authors investigated vaccinating different age groups of the Belgian adult population and stated that the vaccination with PPSV23 (75% coverage) might be considered cost effective with US$88,415/QALY for adults aged 65–74 years and with US$65,468/QALY for those 75–90 years old. The authors further state that the vaccine is cost effective (with willingness to pay [WTP] of US$46,062/QALY) for the 65- to 74-year-olds if there is no reduction in PPSV23-serotype

IPD incidence in the population and the stable vaccine protection lasts longer than 5 years. Of note, the authors applied a conservatively low PPSV23 effectiveness against IPD of 55% taken as the lower value of the given confidence interval reported in the review by Moberley et al. [47].

Adult vaccination with PCV13 compared with no vaccination The studies by Blommaert et al. [26] and Chen et al. [8] evaluated vaccinating adults with PCV13 compared with no vaccination. Both studies showed that PCV13 was unlikely to be cost effective in the presence of the ongoing herd effects of the routine PCV13 childhood vaccination. Most of the ICER estimates reported in these studies lie above US$100,000/QALY. The results reported by Blommaert et al. [26] suggest that vaccinating the elderly ≥ 75 years can be potentially cost effective with an ICER of US$88,842/QALY compared with no vaccination. However, the authors point out that price reductions are required to keep it possibly cost effective when PCV13-preventable PD incidence decreases (24% annually) due to the herd effect. Vaccinating adults aged 50–64 years (ICER of US$287,917/QALY) or 65–74 years (ICER of US$131,104/QALY) was unlikely to be cost effective (with WTP of US$46,062/QALY) at the current prices (PCV13: US$100) unless no herd effect was present and the duration of stable PCV13 protection exceeded 6 years. In the base-case scenario, Blommaert et al. [26] assumed a constant protection for 5 years, which ceased to exist afterwards, and varied the duration of PCV13 protection in relation to the vaccine price in the sensitivity analysis. The results show the distributions of the vaccine prices, which allow keeping the ICER equal to US$46,062/QALY (original €35,000/QALY) with the given duration of protection with and without waning. The results suggest that with a longer duration of protection the vaccine price can be increased.

Chen et al. [8] analyzed the implication of the decline of PCV13 serotype circulation in the adult population in greater detail. The authors investigated a scenario of the indirect reduction in the six additional PCV13 serotypes as it has been observed for the PCV7 serotypes and compared the cost-effectiveness outcomes in this scenario with the estimates obtained under the assumption of potential stabilization seen in the national data. The authors show that compared with the conditions of the stabilization of the indirect effects of the childhood vaccination, ongoing decline of the additional six serotypes covered by PCV13 substantially worsens the cost effectiveness of vaccination for the elderly with PCV13 (US$50,359/QALY vs US$121,288/QALY). The authors emphasize that changes in the serotype distribution caused by the PCV13 childhood programs are critical to the cost effectiveness of PCV13 programs in the elderly.

Adult vaccination with PCV13 compared with vaccination with PPSV23 Stoecker et al. [28] and Willem et al. [10] compared PPSV23 with PCV13 for vaccinating the elderly. The estimated ICER for vaccinating 65-year-olds reported by Stoecker et al. [28] is slightly above US$50,000/QALY. However, Willem et al. [10] showed contrasting ICERs that lie well above US$100,000/QALY.

It is important to note that Stoecker et al. [28] showed that vaccinating at 65 years old was only cost effective (ICER of US$50,891/QALY) in a short period after the introduction of the PCV13 childhood vaccination. The authors analyzed the replacement of PPSV23 with PCV13 for the elderly vaccination in the US and evaluated cost effectiveness of this strategy for the cohort of the year 2013 with PCV13 introduced for the childhood program in 2010. The authors used a single-cohort model and looked at three scenarios of vaccinating the population of 2013 at 50, 60, and 65 years old. They showed that the ICER values rose substantially after 2013, reaching over US$400,000/QALY in 2015, and the PCV13 strategy was dominated. This increase of ICERs after 2015 suggests that a mid- or a long-term vaccination program with PCV13 is unlikely to be cost effective (> US$100,000/QALY). In addition, the authors applied a step-wise waning of PCV13 protection at a rate of 10% every 5 years, resulting in the highest EVPOT in this review.

Willem et al. [10] estimated an ICER for vaccinating 65-year-olds of US$221,970/QALY that can be considered unlikely to be cost effective (relative to a WTP of US$64,773/QALY). The authors performed extensive analyses of different vaccination strategies considering uncertainty surrounding VE, the duration of the protection, vaccine uptake, and initial PD incidence in adults. The authors applied age-specific PCV13 VE obtained from CAPiTA [7], but set it to zero for ≥ 85-year-olds. Comparably to several other studies [8, 9, 26, 30], PPSV23 VE was 56% against IPD but, in contrast, PPSV23 was also assumed to be effective against NBPP with VE of 30.8%. The authors examined different scenarios of VE against NBPP (i.e., when both vaccines are either effective or not effective against NBPP and when only PPSV23 is ineffective). The cost effectiveness of PCV13 was estimated compared with several strategies involving PPSV23: the current program with a low uptake (0.79–3.01%) and a program with an increased PPSV23 uptake (15–25%). The cost effectiveness was analyzed contrasting ICER with different thresholds of WTP (up to US$453,411/QALY). The authors pointed out that PCV13 could become cost effective for people < 75 years of age if a combination of favorable changes around PCV13 occurred, including a substantial (75%) reduction of the vaccine price, an increased duration of protection, and a lower herd effect caused by PCV13 childhood vaccination (i.e., increased disease burden caused by PCV13 serotypes). For the people aged ≥ 75 years, PCV13 remained unlikely to be cost effective in comparison with PPSV23 (ICER of US$438,072/QALY). The higher uptake of PPSV23 would be considerably more efficient relative to the current vaccination situation

with ICERs of US$107,282, US$74,116, and US$67,554 per QALY for the age groups 50–64 years, 65–74 years, and 75–84 years, respectively.

Adult vaccination with a combination of PCV13 and PPSV23 (sequential vaccination) The cost effectiveness of adding PCV13 to PPSV23 in vaccinations for the elderly was analyzed in four selected studies [10, 26, 28, 29]. All of them showed that this strategy was efficacious in reducing the number of cases of IPD and NBPP and related deaths. Blommaert et al. [26], van Hoek and Miller [29] and Willem et al. [10] showed that it was above US$100,000/QALY and was not cost effective. Stoecker et al. [28] showed that the sequential vaccination could possibly be cost effective (with WTP of US$50,000–US$100,000/QALY) in a short period (around 6 years) after the introduction of the PCV13 childhood vaccination.

Stoecker et al. [28] showed an ICER of US$68,078/QALY for the addition of PCV13 to PPSV23 at age 65 years and higher ICERs for vaccinating at age 50 and 60 years with estimates of US$365,482/QALY and US$261,307/QALY, respectively. Similar to the strategy of replacing PPSV23 with PCV13, the ICER for adding PCV13 to PPSV23 was demonstrated to reach over US$250,000/QALY by 2018 for the modeled cohort ≥ 65-year-olds and to be cheaper than the replacement strategy after the first year of the modeling horizon. The dramatic increase in ICER of both strategies over time was driven by the herd effect in the single cohort.

The Belgian studies by Blommaert et al. [26] and Willem et al. [10] showed that the addition of PCV13 to a vaccination scheme with PPSV23 was generally effective but not cost effective at any age. Blommaert et al. [26] stated that this strategy might be cost effective for 65- to 74-year-olds at a WTP of US$46,062/QALY, when the stable PCV13 protection lasted 15 years. Willem et al. [10] concluded that the addition of PCV13 would bring less gain than a high uptake of PPSV23 and would become an expensive strategy with a high ICER. The ICER estimates are US$218,776, US$171,765, and US$201,380 per QALY for the age groups 50–64, 65–74, and 75–84 years, respectively.

Van Hoek and Miller [29] evaluated the cost effectiveness of adding one PCV13 dose to the vaccination with PPSV23 for the elderly aged ≥ 65 years for one cohort of 65-year-olds in England. The authors simulated the disease burden in the cohort from 2016 until death comparing the outcomes of the addition of PCV13 to the current vaccination policy with an uptake of 69% in comparison with the current program without PCV13. They assumed the longest constant duration of PCV13 VE (9 years) among the selected studies, which resulted in a relatively long EVPOT for PCV13, and PPSV23 VE was not reported. The estimated cost-effectiveness ratio for adding PCV13 to PPSV23 was US$375,622/QALY. The authors pointed out that the PCV13 price should be below zero for ICER to be below the threshold of US$29,144/QALY (original £20,000/QALY).

3.3.1.2 PCV13 Serotypes Reached a New Post-vaccination Equilibrium in PD Incidence The Australian studies [8, 9, 30] explored the expected protective impact of PCV13 on PD incidence in the elderly ≥ 65 years and its cost effectiveness when the six additional serotypes included in PCV13 reached stabilization. The new post-vaccination equilibrium was assumed based on the Australian national surveillance data, which showed that after a rapid indirect reduction, the PCV13-type PD incidence among the elderly had stabilized [8, 30]. In these studies, the PCV13-serotype incidence was kept constant.

Adult vaccination with PPSV23 compared with no vaccination The cost-effectiveness of vaccinating the elderly with PPSV23 compared with no program was reported only by Dirmesropian et al. [30], who concluded that the strategy (60% uptake) was not cost effective with an ICER of US$210,800/QALY (vs WTP of US$42,557/QALY). The researchers applied age-specific PPSV23 VE and assumed that the initial constant protection of PPSV23 lasted for 2 years and thereafter linearly declined to zero over 3 years.

Adult vaccination with PCV13 compared with no vaccination The cost effectiveness of vaccinating the elderly with PCV13 was reported to be in the range of US$50,000–US$100,000/QALY and the program could be considered to be potentially cost effective compared with no vaccination. The studies used similar methods in calculation of age effects on VE, waning of the vaccine immunity, and most of the input parameters in the economic evaluation (price, discount rate).

Dirmesropian et al. [30] estimated an ICER of US$62,417/QALY, which is similar to the estimate obtained by Chen et al. [8] for the scenarios with the post-vaccination PCV13-serotype equilibrium (ICER of US$50,359/QALY). Nevertheless, Dirmesropian et al. [30] concluded that the strategy was not cost effective relative to the WTP level of US$42,557/QALY. The authors stated that vaccination with PCV13 could be cost effective when either the vaccine price was below US$33 (A$46) or the duration of PCV13 protection exceeds 15 years.

In another study, Chen et al. [9] demonstrated the importance of modeling the actual age of the vaccine recipients rather than assuming a certain cohort to be vaccinated all at once at a recommended age. The first approach was shown to provide more accurate estimates of the cost effectiveness and the optimal age of vaccine administration (US$59,252/QALY [recommended age scenario] vs US$46,294/QALY [actual age scenario]).

Adult vaccination with PCV13 compared with vaccination with PPSV23 Dirmesropian et al. [30] also concluded that PCV13 was cost effective versus PPSV23 with an

ICER of US$25,038/QALY (vs WTP of $42,557/QALY). The authors pointed out that PCV13 was favored due to the longer duration of protection and higher VE against IPD and NBPP. The assumption that PPSV23 has no efficacy against non-invasive PD was tested in the sensitivity analyses, which resulted in larger benefits of PPSV23 and a substantial reduction in differences between ICERs.

3.3.2 Childhood Vaccination: PCV10 is Replaced with PCV13

Thorrington et al. [32] specified a hypothetical scenario of switching from PCV10 to PCV13 in the infant vaccination program and evaluated adult vaccination with PCV13 and/or PPSV23 in the Netherlands. The authors examined different scenarios of vaccinating 50% of adults over 60 years of age in combination with infant vaccination with PCV13 in comparison to the current vaccination scheme of no adult vaccination and PCV10 infant immunization. The authors projected the evolution of serotype epidemiology of IPD in Dutch adults with a routine infant vaccination with PCV10 and with PCV13, respectively. Thorrington et al. [32] showed that the strategies of vaccinating the elderly with PPSV23 with or without re-vaccination were cost effective relative to WTP of US$25,560/QALY, with vaccinating at age 70 being the most cost-effective scenario (ICER of US$7925/QALY). Vaccinating the elderly with PCV13 was shown to be more expensive, generating a higher ICER. The authors pointed out that switching to PCV13 for the infant vaccination was a rather inexpensive strategy having a beneficial health impact for the elderly as well.

3.3.3 Childhood Vaccination with PCV10

The earliest study was conducted by Mangen et al. [25] in 2015 for the Netherlands, where PCV7 had been replaced with PCV10 in the childhood pneumococcal vaccination program in 2011. The authors evaluated age- and risk-group-specific strategies of vaccinating adults aged 65–74 years with PCV13 in comparison with no vaccination from a societal perspective. Vaccination coverage varied with the health-risk group (63.9% for low-risk groups; 81.5% for medium- and high-risk groups). The resulting ICER was US$12,003/QALY for vaccinating those aged 65–74 years with a single dose of PCV13. Relative to the WTP level of US$105,900/QALY, the authors inferred that vaccination strategies with PCV13 were cost effective and vaccinating 65- to 74-year-old high-risk individuals was cost saving in the Netherlands.

3.3.4 Childhood Vaccination: PCV13 is Replaced with PCV10

Willem et al. [10] also investigated the potential impact of replacing PCV13 with PCV10 in the infant vaccination on serotype distribution. Motivation for this analysis was that PCV10 had been introduced in two regions of the country, which potentially could induce reoccurrence of three PCV13 serotypes not included in PCV10 in the elderly population. The authors analyzed a 'quick' (within 7 years) and a 'slow' (within 15 years) scenario of the potential return of PCV13 serotype incidence to the level of 2015 (current state). When PCV13 is replaced with PCV10 in the childhood vaccination, the relapse of PCV13-minus-PCV10 serotype incidence can make adult vaccination with PCV13 more beneficial.

4 Discussion

In this study, we analyzed the methods applied to model vaccine effectiveness over time as well as the indirect effects of PCV infant vaccination. In addition, we summarized the evidence of the cost effectiveness of the elderly pneumococcal vaccination in the presence of the childhood vaccination with the higher-valent PCVs. We applied very strict inclusion criteria on the assumptions and methodological choices made in the modeling of the vaccine effects. Overall, out of the 28 full-text economic evaluations that were reviewed, we selected 13 for the quality assessment with EVIDEM and included nine evaluations of the higher quality group to present the cost-effectiveness estimates.

4.1 Initial Vaccine Effectiveness

Despite our strict selection criteria regarding the input parameters for VE, we found substantial heterogeneity in the values used in the selected studies. In the case of PCV13, in order to restrain variation in the applied VE parameters we only selected studies that referred to the CAPiTA trial [7] to inform VE parameters. For PPSV23, we observed a greater variation originating from the chosen sources and applied age and health effects. Studies referencing Shapiro et al. [58] and Moberley et al. [47, 53] were seen to apply a higher PPSV23 effectiveness against IPD. In contrast to the majority of these studies, Blommaert et al. [26] applied the lowest value (55%) of the confidence interval provided by Moberley et al. [47]. This value was considerably lower but similar to VE of 56–58% used in the models referencing the review by Andrews et al. [15]. A few studies also included PPSV23 effectiveness against NBPP either in their baseline or sensitivity analyses informing the VE parameter with the data from cohort studies conducted in Spain [48, 57, 65, 66]. We found between- and (in some cases) within-study

differences in the magnitude of applied age effects on the VE.

So far, the study of van Werkhoven et al. [50, 51] is the only analysis that explored vaccine-age-interaction effects of PCV13 among the elderly. The authors report statistically significant interaction effects for pneumococcal pneumonia (including invasive and non-invasive diseases). However, the applied statistical model showed a relatively poor fit for the age group ≥ 85 years, in which very few disease episodes occurred [25, 51]. Excluding this age group from the analysis, the vaccine-age-interaction was not statistically significant [25, 51]. Several observational studies [12, 15, 66–68] indicate vaccine-age interaction effects for PPSV23 but these have not been further investigated, although Djennad et al. [67] reported that differences in PPSV23 VE against vaccine-type IPD were significant between different age groups. Based on the current evidence about the vaccine-age-interaction effects for PCV13 and PPSV23, both age-dependent and age-independent approaches to VE can be justified and both scenarios should be evaluated in cost-effectiveness analyses. Of note, when estimating single-age or age-group-specific VE for PPSV23 based on existing observational studies, it should be considered that most observational studies stratify age groups according to the age at occurrence of the diseases and not according to the age at vaccination.

4.2 Duration of Vaccine Protection and Waning Patterns

The absence of robust empirical evidence about the duration of vaccine protection led to a great variation of methodological approaches to address this uncertainty. The majority of the studies shared the concept of composing the duration of vaccine protection from a period of stable immunity equal to VE at administration, followed by a period of waning protection. The CAPiTA trial [7] showed no waning of PCV13 effectiveness over the study period of 4–5 years and most of the studies in this review applied 4–5 years of constant protection and made assumptions regarding the subsequent waning pattern. For PPSV23, a 2- to 5-year period of stable protection was frequently used. Overall, the majority of the studies reflected in the assumptions the implication that PCV13 induced a more profound immune response than PPSV23 [7] and applied a longer-lasting protection of PCV13. A broadly used approach to modeling the waning pattern was a linear or a step-wise linear decline to 0% effectiveness over some period of time, with the annual waning rates varying across the studies. A more conservative approach, which might ease a comparative analysis of the vaccines, was to set the same duration of the protection for both vaccines, which was done in one study in this review [26]. However, the conjugate vaccine is expected to protect for longer due to the stronger vaccine-induced response [16].

In addition, upon the comparison of the reported VE values and constructed waning patterns, we calculated expected vaccine protection over time (EVPOT) to facilitate comparison of the combination of these constituents of vaccine protection between and within the studies. EVPOT was estimated by computing the area under the curve of VE over time and represents a measure of years of vaccine protection adjusted for the initial VE value, that is, it is composed of multiplicative effects of the initial VE and the applied years of waning protection. Although EVPOT allows for the comparison of modeled vaccine effects between the studies using a single value, this approach has certain limitations. Firstly, upon combining two constituents of the vaccine effects into a single value, the information about the effects and magnitude of each of them becomes hidden; therefore, we reported both constituents of EVPOT separately for each reviewed study. Secondly, when a relatively long waning period is applied, EVPOT can lead to a biased representation of the vaccine effects, which are actually simulated in the modeling. In particular, the waning patterns with a very long tail to the right may result in high EVPOT but substantial vaccine benefits resulting from the assumed long protection may not actualize in the projection, for instance, due to high mortality rates or due to the herd effect of infant vaccination. To avoid this limitation, we chose a cut-off point of 20 years since vaccination to calculate EVPOT. An alternative method of comparison of applied vaccine effects is the calculation of the half-time duration; that is, estimation of the time since vaccination at which VE is reduced to 50% of its initial value [69]. This measure, however, may introduce a bias towards the waning patterns that start with a slow waning of the initial VE followed by a rapid waning phase as compared with waning with constant rates. This, however, reflects the fact that the present effects have more value than the future effects for instance, due to mortality, quality of life decreasing with age, discounting of health outcomes and costs, and the herd effects. This preference for a slow followed by a rapid waning phase may provide a different conclusion about the outcomes of the vaccination over time as compared with the calculation of the area under the curve; that is, a vaccine may have longer half-time duration but a lower area under the curve. Furthermore, it does not include the impact of the initial VE and the combined effect of initial VE and the waning function.

4.3 Indirect Effects of Infant Vaccination

We observed different methodological approaches for predicting the serotype evolution. The first was to start from equilibrium of the childhood PCV-type serotypes in the elderly IPD incidence and assume no further herd effects, which was done in the Australian studies [8, 9, 30] and one Dutch study [25]. This approach is reasonable when

the national epidemiological data sufficiently indicates that new post-PCV equilibrium has been reached or if there are no net indirect changes in the preventable PD incidence. It is important to note that Australia implemented a 3 + 0 schedule of the PCV13 program in children that is unique among high-income countries. The reported possible consequences of the schedule without a booster dose include increased PCV13 breakthrough cases and decreased herd effects in PCV13-serotype-induced IPD incidence in the older population [17]. The unique epidemiological settings of Australia make it difficult to transfer the cost-effectiveness projections reported in the Australian studies to other countries.

The second method was to increase the herd effect of PCV13 serotypes step-wise and assume that the maximum reduction of the IPD incidence was reached between years 5 and 7 of the time horizon [27, 31]. A slight variation of this approach was found in two Belgian studies [10, 26], which applied an average annual decline of the PCV13-type incidence without the successive steady state. Finally, four studies predicted forward the distribution of the six additional serotypes contained in PCV13 (PCV13-minus-PCV7). The methodological choice was either to assume that the six serotypes followed a similar decline as the PCV7 serotypes followed by stabilization [24, 28, 29] or to predict a decline in the incidence using a regression equation estimated on the data for the previous years and assume stabilization after some years [33].

Another important indirect effect of the PCV childhood vaccination is the vaccine-induced serotype replacement that might counteract the beneficial impact of the herd effect in the unvaccinated population. Not all studies that modeled the herd effect included the serotype replacement. We found five studies [10, 24, 26, 28, 32] that reported the serotype replacement. The methodological approaches were either to apply an increase in non-vaccine-type PD incidence modeled as a fixed proportion of the reduction in the IPD incidence due to the herd effect or to project the effects of childhood vaccination with PCV7. It is important to note that if the pneumococcal vaccine under evaluation contains serotypes that are not included in the conjugated vaccine used for the childhood vaccination, the replacement effects potentially caused by these additional serotypes should be examined and incorporated into the model.

Extrapolation of the historical effects caused by PCV7 vaccination onto the six additional serotypes in PCV13 should be done with caution as pointed out by Chen et al. [8]. This statement was based on the findings that the circulation of the six additional serotypes declined in a shorter period than PCV7 serotypes in Australia, which may lead to a considerable shift in the steady-state predictions. However, post-PCV13-vaccination studies showed the persistence of serotype 3 in the population; that is, PCV-13 infant immunization has no or very limited indirect effect on the IPD incidence caused by serotype 3 [70]. Recently published epidemiological data also indicates that serotype 19A, after a substantial decrease due to the herd effect, may stabilize at a low level [71, 72]. Therefore, the common approach to group the serotypes by vaccine (e.g., PCV7 serotypes, PCV13 serotypes, PCV13-minus-PCV7 serotypes) may be misleading and can result in poor predictions, underestimating the remaining burden of pneumococcal diseases caused by PCV13 serotypes. The application of the serotype-specific epidemiology of invasive and non-invasive PD in the model allows a more realistic estimation of the vaccination effects. Any-serotype and all-cause approaches lead to a false presentation of the indirect effects on the selected groups of serotypes, particularly PCV13-type (see ESM file S1: section 1.2.2), favoring the outcomes of the elderly vaccination and improving its cost effectiveness. It is important to note that assumptions and input data used to inform a decision-analytic model become outdated with time and the results of an economic evaluation have to be updated when new information regarding country-specific *S. pneumoniae* epidemiology becomes available.

In addition, the studies by Stoecker et al. [28] and Chen et al. [9] demonstrated that model type (single cohort vs multi-cohort) substantially affected the results when time-varying serotype epidemiology is to be modeled. The authors point out that single-cohort models do not produce valid ICERs over a series of years because they do not capture variation of the serotype distribution, which in turn are differently affected by VE. The resulting ICERs over a set of calendar years in the papers by Chen et al. [9] and Stoecker et al. [28] show substantial variation between the cohorts that are vaccinated in different calendar years. Single-cohort models provide valid results only when epidemiological equilibrium has been reached before the start of the model period. Otherwise, when the dynamic indirect effects are present, application of a multi-cohort model is required to capture the ongoing changes in the PD incidence.

Furthermore, in this review we did not identify dynamic transmission models and application of PCV13 VE against the bacterial nasopharyngeal carriage. Currently, there is little empirical evidence on the protective effects of vaccine-induced reduction of the bacterial carriage in the elderly. Van Deursen et al. [73] reported that PCV13 induced a small and short-lived decline in the vaccine-type nasopharyngeal carriage in people aged ≥ 65 years. This may lead to additional herd effects with the elderly vaccination, which can be particularly beneficial in the communities with higher concentration of the elderly [74].

Overall, these considerations should be seen as relevant for the decision-making process and the studies that aim to support the decision outcomes should describe their methodological choices and assumptions and provide a transparent reporting of the disease incidence rates for all relevant

serotype groups over the modeling time horizon or until a new post-vaccination equilibrium is reached.

4.4 Cost Effectiveness

The current evidence about the cost effectiveness of pneumococcal vaccination of the elderly in the presence of a higher valent PCV infant vaccination program is inconclusive. Reviewing the studies with a higher relevance and validity score, we found predominant evidence that vaccinating the elderly with PCV13 is not cost effective when an ongoing decline in the incidence of PCV13-type PD is modeled either until extinction of PCV13 serotypes or until a very low PCV13 PD incidence level is reached. However, the current epidemiologic evidence suggest that PCV13 IPD incidence initially substantially declines but then persists on a moderate level in the presence of PCV13 infant vaccination [67, 70–72, 75]. In the Australian studies [8, 9, 30], similar stabilization of PCV13 serotypes was applied and ICERs of PCV13 versus no vaccination were in the range of US$50,000–US$100,000/QALY. However, at the time of the evaluations, the unique 3 + 0 PCV13 infant vaccination schedule was applied. Jayasinghe et al. [17] found fast waning of PCV13 effectiveness under this schedule, which may have resulted in a higher persistent PCV13 PD incidence compared with the settings of more commonly used vaccination schedules (2 + 1 or 3 + 1). Thorrington et al. [32], who also modeled the moderate persistent incidence, reported ICERs of US$50,000–US$100,000/QALY for PCV13 versus no vaccination but the effects of the replacement of PCV10 with PCV13 in the infant vaccination was based on many assumptions. In contrast to Dirmesropian et al. [30], Thorrington et al. [32] found that PPSV23 showed better value for money than PCV13 in the vaccination of the elderly. A key difference between the studies was the application of a moderate PPSV23 VE against NBPP in the study by Thorrington et al. [32] as compared with the assumption of no protective effects by Dirmesropian et al [30].

The findings by Blommaert et al. [26], Thorrington et al. [32], and Willem et al. [10] indicate that PPSV23 is likely to be a cost-effective vaccination strategy in all reviewed epidemiologic scenarios if it is at least moderately effective against NBPP and the expected duration of protection lasts at least 3–4 years. The outcomes of the vaccination with PPSV23 were less affected by the indirect effects of the childhood vaccination due to the wide serotype coverage of the vaccine, but the childhood vaccination still played a crucial role for the vaccination benefits. In the absence of a protective effect against NBPP, evidence for the cost effectiveness of PPSV23 is not conclusive. Childhood vaccination with PCV10 makes the elderly vaccination with PCV13 more attractive due to the three additional serotypes preventable by PCV13.

Currently, there is a lack of studies that model the important PCV13 serotypes such as serotype 3 separately from other groups of serotypes when evaluating pneumococcal vaccination of the elderly in the presence of a PCV13 infant vaccination. Besides the accurate presentation of epidemiologic effects, there are still issues regarding the effectiveness of both vaccines (PCV13 and PPSV23) against serotype 3 [15, 17, 67, 76, 77], which may also require the separation of serotype 3 from other groups in the presence of PCV10 infant vaccination to investigate scenarios with the reduced vaccine effectiveness [78].

5 Conclusion

To summarize, in this review we found major differences in the methods and assumptions applied in the modeling of VE and the indirect effects of the childhood vaccination with the higher valent vaccines (PCV10 and PCV13). Results of the cost-effectiveness analyses are largely determined by the predictions of PD incidence and the estimates of pneumococcal VE over time on which they are based. Insight into the modeling of these processes can help to rationally interpret obtained cost-effectiveness estimates and to understand the variation of conclusions among the studies. It is also important to take into consideration all dimensions of economic evaluation that may drive the ICER estimates; these include characteristics of vaccination strategy (age range, dose and uptake), vaccine price, cost per PD case, utility estimates, modeling time horizon, and discount rates. Taken together, country-specific *S. pneumoniae* epidemiology, vaccination strategy, and country-specific economic inputs require the development of a decision-analytic model specific for this country. Any comparisons between outcomes of models from different countries should be made with caution due to the large number of parameters that determine the results.

Overall, a major pneumococcal vaccination campaign for the elderly is largely resource-consuming and with all the other social and public health challenges at hand the opportunity cost of such a vaccination campaign may be high. For this reason, the need for well-designed modeling studies that produce representative and non-biased cost-effectiveness estimates cannot be overemphasized.

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Compliance with Ethical Standards

Data availability statement The data used in the present review can be found in the studies cited in the main and supplemental text. All other data generated during the review are available from the corresponding author upon request.

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Research involving human participants and/or animals Not applicable.

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References

1. Tin Tin Htar M, Christopoulou D, Schmitt H-J. Pneumococcal serotype evolution in Western Europe. BMC Infect Dis. 2015;15:419. https://doi.org/10.1186/s12879-015-1147-x.
2. Shiri T, Datta S, Madan J, Tsertsvadze A, Royle P, Keeling MJ, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:e51–9. https://doi.org/10.1016/S2214-109X(16)30306-0.
3. Ogilvie I, Khoury AE, Cui Y, Dasbach E, Grabenstein JD, Goetghebeur M. Cost-effectiveness of pneumococcal polysaccharide vaccination in adults: a systematic review of conclusions and assumptions. Vaccine. 2009;27:4891–904. https://doi.org/10.1016/j.vaccine.2009.05.061.
4. Dirmesropian S, Wood JG, MacIntyre CR, Newall AT. A review of economic evaluations of 13-valent pneumococcal conjugate vaccine (PCV13) in adults and the elderly. Hum Vaccin Immunother. 2015;11:818–25. https://doi.org/10.1080/21645515.2015.1011954.
5. Nishikawa AM, Sartori AMC, Mainardi GM, Freitas AC, Itria A, Novaes HMD, de Soárez PC. Systematic review of economic evaluations of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in individuals 60 years of age or older. Vaccine. 2018;36:2510–22. https://doi.org/10.1016/j.vaccine.2018.03.070.
6. Porchia BR, Bonanni P, Bechini A, Bonaccorsi G, Boccalini S. Evaluating the costs and benefits of pneumococcal vaccination in adults. Expert Rev Vaccines. 2017;16:93–107. https://doi.org/10.1080/14760584.2017.1242419.
7. Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–25. https://doi.org/10.1056/NEJMoa1408544.
8. Chen C, Beutels P, Newall AT. Evolution over time in the cost-effectiveness of pneumococcal conjugate vaccine (PCV13) in older Australians due to herd protection from infant vaccination. Vaccine. 2018;36:2057–60. https://doi.org/10.1016/j.vaccine.2018.03.006.
9. Chen C, Wood JG, Beutels P, Menzies R, MacIntyre CR, Dirmesropian S, et al. The role of timeliness in the cost-effectiveness of older adult vaccination: a case study of pneumococcal conjugate vaccine in Australia. Vaccine. 2018;36:1265–71. https://doi.org/10.1016/j.vaccine.2018.01.052.
10. Willem L, Blommaert A, Hanquet G, Thiry N, Bilcke J, Theeten H, et al. Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. Hum Vaccin Immunother. 2018. https://doi.org/10.1080/21645515.2018.1428507.
11. Le Polain De Waroux O, Flasche S, Prieto-Merino D, Goldblatt D, Edmunds WJ. The efficacy and duration of protection of pneumococcal conjugate vaccines against nasopharyngeal carriage: a meta-regression model. Pediatr Infect Dis J. 2015;34:858–64. https://doi.org/10.1097/inf.0000000000000717.
12. Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis. 2017;17:313–21. https://doi.org/10.1016/S1473-3099(17)30049-X.
13. Rudnick W, Liu Z, Shigayeva A, Low DE, Green K, Plevneshi A, et al. Pneumococcal vaccination programs and the burden of invasive pneumococcal disease in Ontario, Canada, 1995–2011. Vaccine. 2013;31:5863–71. https://doi.org/10.1016/j.vaccine.2013.09.049.
14. Gutiérrez Rodríguez MA, Ordobás Gavín MA, García-Comas L, Sanz Moreno JC, Córdoba Deorador E, Lasheras Carbajo MD, Taveira Jiménez JA, Martín Martínez F, Iniesta Fornies D, Arce Arnaez A. Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008–2011. 2014. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES2014.19.40.20922. Accessed 24 Oct 2018.
15. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30:6802–8. https://doi.org/10.1016/j.vaccine.2012.09.019.
16. Svensson T, Kättström M, Hammarlund Y, Roth D, Andersson P-O, Svensson M, et al. Pneumococcal conjugate vaccine triggers a better immune response than pneumococcal polysaccharide vaccine in patients with chronic lymphocytic leukemia A randomized study by the Swedish CLL group. Vaccine. 2018;36:3701–7. https://doi.org/10.1016/j.vaccine.2018.05.012.
17. Jayasinghe S, Chiu C, Quinn H, Menzies R, Gilmour R, McIntyre P. Effectiveness of 7- and 13-valent pneumococcal conjugate vaccines in a schedule without a booster dose: a 10-year observational study. Clin Infect Dis. 2018;67:367–74. https://doi.org/10.1093/cid/ciy129.
18. Henriques-Normark B, Tuomanen EI. The pneumococcus: epidemiology, microbiology, and pathogenesis. Cold Spring Harb Perspect Med. 2013. https://doi.org/10.1101/cshperspect.a010215.
19. World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. 2008. http://www.who.int/iris/handle/10665/69981. Accessed 14 Mar 2018.
20. Goetghebeur MM, Wagner M, Khoury H, Levitt RJ, Erickson LJ, Rindress D. Evidence and value: impact on decisionmaking—the EVIDEM framework and potential applications. BMC Health Serv Res. 2008;8:270. https://doi.org/10.1186/1472-6963-8-270.
21. OECD. Inflation (CPI) (indicator): OECD; 2017. https://data.oecd.org/price/inflation-cpi.htm. Accessed 3 Sept 2018.
22. OECD. Purchasing power parities (PPP) (indicator): OECD; 2017. https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. Accessed 3 Sept 2018.
23. OECD. Exchange rates (indicator): OECD; 2017. https://data.oecd.org/conversion/exchange-rates.htm. Accessed 3 Sept 2018.
24. Jiang Y, Gauthier A, Annemans L, van der Linden M, Nicolas-Spony L, Bresse X. Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine

(PPV23) in Germany. Expert Rev Pharmacoecon Outcomes Res. 2012;12:645–60. https://doi.org/10.1586/erp.12.54.
25. Mangen M-JJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46:1407–16. https://doi.org/10.1183/13993003.00325-2015.
26. Blommaert A, Bilcke J, Willem L, Verhaegen J, Goossens H, Beutels P. The cost-effectiveness of pneumococcal vaccination in healthy adults over 50: an exploration of influential factors for Belgium. Vaccine. 2016;34:2106–12. https://doi.org/10.1016/j.vaccine.2016.03.003.
27. Rodriguez Gonzalez-Moro JM, Menendez R, Campins M, Lwoff N, Oyaguez I, Echave M, et al. Cost effectiveness of the 13-valent pneumococcal conjugate vaccination program in chronic obstructive pulmonary disease patients aged 50 + years in Spain. Clin Drug Investig. 2016;36:41–53. https://doi.org/10.1007/s40261-015-0345-z.
28. Stoecker C, Kim L, Gierke R, Pilishvili T. Incremental cost-effectiveness of 13-valent pneumococcal conjugate vaccine for adults age 50 years and older in the United States. J Gen Intern Med. 2016;31:901–8. https://doi.org/10.1007/s11606-016-3651-0.
29. van Hoek AJ, Miller E. Cost-effectiveness of vaccinating immunocompetent/= 65 year olds with the 13-valent pneumococcal conjugate vaccine in England. PLoS One. 2016;11:e0149540. https://doi.org/10.1371/journal.pone.0149540.
30. Dirmesropian S, Wood JG, MacIntyre CR, Beutels P, McIntyre P, Menzies R, et al. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) in older Australians. Vaccine. 2017;35:4307–14. https://doi.org/10.1016/j.vaccine.2017.06.085.
31. Heo JY, Seo YB, Choi WS, Lee J, Noh JY, Jeong HW, et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLoS One. 2017;12:e0177342. https://doi.org/10.1371/journal.pone.0177342.
32. Thorrington D, van Rossum L, Knol M, de Melker H, Rümke H, Hak E, van Hoek AJ. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS One. 2018;13:e0192640. https://doi.org/10.1371/journal.pone.0192640.
33. Kuchenbecker U, Chase D, Reichert A, Schiffner-Rohe J, Atwood M. Estimating the cost-effectiveness of a sequential pneumococcal vaccination program for adults in Germany. PLoS One. 2018;13:e0197905. https://doi.org/10.1371/journal.pone.0197905.
34. Merito M, Giorgi Rossi P, Mantovani J, Curtale F, Borgia P, Guasticchi G. Cost-effectiveness of vaccinating for invasive pneumococcal disease in the elderly in the Lazio region of Italy. Vaccine. 2007;25:458–65. https://doi.org/10.1016/j.vaccine.2006.08.005.
35. Rozenbaum MH, Hak E, van der Werf TS, Postma MJ. Results of a cohort model analysis of the cost-effectiveness of routine immunization with 13-valent pneumococcal conjugate vaccine of those aged or = 65 years in the Netherlands. Clin Ther. 2010;32:1517–32. https://doi.org/10.1016/j.clinthera.2010.06.016.
36. Akin L, Kaya M, Altinel S, Durand L. Cost of pneumococcal infections and cost-effectiveness analysis of pneumococcal vaccination at risk adults and elderly in Turkey. Hum Vaccin. 2011;7:441–50.
37. Neto JT, de Araujo GTB, Gagliardi A, Pinho A, Durand L, Fonseca M. Cost-effectiveness analysis of pneumococcal polysaccharide vaccination from age 60 in Sao Paulo State, Brazil. Hum Vaccin. 2011;7:1037–47. https://doi.org/10.4161/hv.7.10.15987.
38. Grzesiowski P, Aguiar-Ibanez R, Kobryn A, Durand L, Puig P-E. Cost-effectiveness of polysaccharide pneumococcal vaccination in people aged 65 and above in Poland. Hum Vaccin Immunother. 2012;8:1382–94. https://doi.org/10.4161/hv.21571.
39. Kuhlmann A, Theidel U, Pletz MW, von der Schulenburg J-MG. Potential cost-effectiveness and benefit-cost ratios of adult pneumococcal vaccination in Germany. Health Econ Rev. 2012;2:4. https://doi.org/10.1186/2191-1991-2-4.
40. Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012;307:804–12. https://doi.org/10.1001/jama.2012.169.
41. Weycker D, Sato R, Strutton D, Edelsberg J, Atwood M, Jackson LA. Public health and economic impact of 13-valent pneumococcal conjugate vaccine in US adults aged ≥ 50 years. Vaccine. 2012;30:5437–44. https://doi.org/10.1016/j.vaccine.2012.05.076.
42. Chen J, O'Brien MA, Yang HK, Grabenstein JD, Dasbach EJ. Cost-effectiveness of pneumococcal vaccines for adults in the United States. Adv Ther. 2014;31:392–409. https://doi.org/10.1007/s12325-014-0115-y.
43. Liguori G, Parlato A, Zamparelli AS, Belfiore P, Galle F, Di Onofrio V, et al. Adult immunization with 13-valent pneumococcal vaccine in Campania region, South Italy: an economic evaluation. Hum Vaccin Immunother. 2014;10:492–7. https://doi.org/10.4161/hv.26888.
44. Ordonez JE, Orozco JJ. Cost-effectiveness analysis of pneumococcal conjugate vaccine 13-valent in older adults in Colombia. BMC Infect Dis. 2014;14:172. https://doi.org/10.1186/1471-2334-14-172.
45. de Soarez PC, Sartori AMC, Freitas AC, Nishikawa AM, Novaes HMD. Cost-effectiveness analysis of universal vaccination of adults aged 60 years with 23-valent pneumococcal polysaccharide vaccine versus current practice in Brazil. PLoS One. 2015;10:e0130217. https://doi.org/10.1371/journal.pone.0130217.
46. Zhao D, Gai Tobe R, Cui M, He J, Wu B. Cost-effectiveness of a 23-valent pneumococcal polysaccharide vaccine immunization programme for the elderly in Shanghai, China. Vaccine. 2016;34:6158–65. https://doi.org/10.1016/j.vaccine.2016.11.003.
47. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008. https://doi.org/10.1002/14651858.cd000422.pub2.
48. Vila-Córcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodríguez T, Llor C. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis. 2006;43:860–8. https://doi.org/10.1086/507340.
49. Rodriguez-Barradas MC, Goulet J, Brown S, Goetz MB, Rimland D, Simberkoff MS, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. Clin Infect Dis. 2008;46:1093–100. https://doi.org/10.1086/529201.
50. van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJM. The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly. Clin Infect Dis. 2015;61:1835–8. https://doi.org/10.1093/cid/civ686.
51. van Werkhoven CH, Huijts SM, Bolkenbaas M. 13-valent pneumococcal conjugate vaccine efficacy is declining with old age: results from an exploratory analysis of the CAPiTAtrial. In: IDWeek: Philadelphia < 2014. Abstract #1099.
52. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349:1341–8. https://doi.org/10.1056/NEJMoa035060.
53. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013. https://doi.org/10.1002/14651858.cd000422.pub3.
54. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009;180:48–58. https://doi.org/10.1503/cmaj.080734.

55. French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet. 2000;355:2106–11.
56. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (ppv23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS One. 2017;12:e0169368. https://doi.org/10.1371/journal.pone.0169368.
57. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, Gomez-Bertomeu F, Figuerola-Massana E, Raga-Luria X, Hospital-Guardiola I. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged ≥60 years: 3 years of follow-up in the CAPAMIS study. Clin Infect Dis. 2014;58:909–17. https://doi.org/10.1093/cid/ciu002.
58. Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325:1453–60. https://doi.org/10.1056/NEJM199111213252101.
59. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: a systematic review and meta-analysis. Vaccine. 2016;34:1540–50. https://doi.org/10.1016/j.vaccine.2016.02.024.
60. Ortqvist A, Hedlund J, Burman LA, Elbel E, Höfer M, Leinonen M, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. Lancet. 1998;351:399–403.
61. Smith KJ, Zimmerman RK, Lin CJ, Nowalk MP, Ko F-S, McEllistrem MC, Roberts MS. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine. 2008;26:1420–31. https://doi.org/10.1016/j.vaccine.2008.01.007.
62. Fry AM, Zell ER, Schuchat A, Butler JC, Whitney CG. Comparing potential benefits of new pneumococcal vaccines with the current polysaccharide vaccine in the elderly. Vaccine. 2002;21:303–11.
63. Knol MJ, Wagenvoort GHJ, Sanders EAM, Elberse K, Vlaminckx BJ, de Melker HE, van der Ende A. Invasive pneumococcal disease 3 years after introduction of 10-valent pneumococcal conjugate vaccine, the Netherlands. Emerg Infect Dis. 2015;21:2040–4. https://doi.org/10.3201/eid2111.140780.
64. Pletz MW, Ewig S, Rohde G, Schuette H, Rupp J, Welte T, et al. Impact of pneumococcal vaccination in children on serotype distribution in adult community-acquired pneumonia using the serotype-specific multiplex urinary antigen detection assay. Vaccine. 2016;34:2342–8. https://doi.org/10.1016/j.vaccine.2016.03.052.
65. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, Ochoa-Gondar O, de Diego C, Valdivieso A, et al. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. Vaccine. 2009;27:1504–10. https://doi.org/10.1016/j.vaccine.2009.01.013.
66. Gutiérrez Rodríguez MA, Ordobás Gavín MA, García-Comas L, Sanz Moreno JC, Córdoba Deorador E, Lasheras Carbajo MD, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008–2011. Eurosurveillance. 2014. https://doi.org/10.2807/1560-7917.es2014.19.40.20922.
67. Djennad A, Ramsay ME, Pebody R, Fry NK, Sheppard C, Ladhani SN, Andrews NJ. Effectiveness of 23-valent polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. EClinicalMedicine. 2018;6:42–50. https://doi.org/10.1016/j.eclinm.2018.12.007.
68. Wright LB, Hughes GJ, Chapman KE, Gorton R, Wilson D. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in people aged 65 years and over in the North East of England, April 2006–July 2012. Trials Vaccinol. 2013;2:45–8. https://doi.org/10.1016/j.trivac.2013.09.004.
69. Bilcke J, Verelst F, Beutels P. Sponsorship bias in base-case values and uncertainty bounds of health economic evaluations? A systematic review of herpes zoster vaccination. Med Decis Making. 2018;38:730–45. https://doi.org/10.1177/0272989X18776636.
70. Slotved H-C, Dalby T, Harboe ZB, Valentiner-Branth P, Casadevante VFD, Espenhain L, et al. The incidence of invasive pneumococcal serotype 3 disease in the Danish population is not reduced by PCV-13 vaccination. Heliyon. 2016;2:e00198. https://doi.org/10.1016/j.heliyon.2016.e00198.
71. Southern J, Andrews N, Sandu P, Sheppard CL, Waight PA, Fry NK, et al. Pneumococcal carriage in children and their household contacts six years after introduction of the 13-valent pneumococcal conjugate vaccine in England. PLoS One. 2018;13:e0195799. https://doi.org/10.1371/journal.pone.0195799.
72. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis. 2018;18:441–51. https://doi.org/10.1016/S1473-3099(18)30052-5.
73. van Deursen AMM, van Houten MA, Webber C, Patton M, Scott D, Patterson S, et al. The impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal carriage in the community acquired pneumonia immunization trial in adults (CAPiTA) study. Clin Infect Dis. 2018;67:42–9. https://doi.org/10.1093/cid/ciy009.
74. Cafiero-Fonseca ET, Stawasz A, Johnson ST, Sato R, Bloom DE. The full benefits of adult pneumococcal vaccination: a systematic review. PLoS One. 2017;12:e0186903. https://doi.org/10.1371/journal.pone.0186903.
75. Pilishvili T, Gierke R, Farley M, Schaffner W, Thomas A, Reingold A, et al. Direct and Indirect impact of 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease (IPD) among children and adults in the U.S. Open Forum Infect Dis. 2017;4:S66–7. https://doi.org/10.1093/ofid/ofx162.158.
76. Vila-Corcoles A, Ochoa-Gondar O. Pneumococcal conjugate vaccination: correlates of protection. Lancet Infect Dis. 2014;14:784–6. https://doi.org/10.1016/S1473-3099(14)70849-7.
77. Domínguez Á, Ciruela P, Hernández S, García-García JJ, Soldevila N, Izquierdo C, et al. Effectiveness of the 13-valent pneumococcal conjugate vaccine in preventing invasive pneumococcal disease in children aged 7–59 months. A matched case-control study. PLoS One. 2017;12:e0183191. https://doi.org/10.1371/journal.pone.0183191.
78. Falkenhorst G, Remschmidt C, Harder T, Wichmann O, Glodny S, Hummers-Pradier E, et al. Background paper to the updated pneumococcal vaccination recommendation for older adults in Germany. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2016;59:1623–57. https://doi.org/10.1007/s00103-016-2466-9.

S1. Methods

1. Constituents of vaccination effects: a theoretical framework

In the following, we describe key parameters which are essential for the qualitative assessment and/or comparison of effectiveness and cost-effectiveness outcomes of health economic evaluations of adult pneumococcal vaccination.

1.1. Effectiveness against vaccine-type pneumococcal diseases

1.1.1. Maximal vaccine effectiveness

We define the maximal vaccine effectiveness (MVE) as the effectiveness at the time of administration (or shortly after) before the occurrence of waning immunity. Clinical trials typically report average vaccine effectiveness over a defined period of time (study follow-up). Therefore, if the follow-up time of a modeling study is rather long and a strong waning rate of effectiveness is assumed, the maximal vaccine effectiveness is typically higher than the average effectiveness reported in the clinical study.

1.1.2. Waning pattern

The effect of a vaccine is dependent on the maximal vaccine effectiveness and the duration of the protection, i.e., a vaccine with a low MVE but a long duration of protection might result in a similar number of prevented cases than a vaccine with a high MVE but a short duration of protection. To make these input parameters of the different models easily comparable, we calculated two different indices: *years of full protection* and *expected vaccine protection over time*.

Years of full protection approach looks at each year after the initial year of immunization and calculates the percentage of the remaining vaccine effectiveness compared to the baseline vaccine effectiveness. For example, a baseline vaccine effectiveness of 0.80 in the first year and 0.40 in the second year would yield 1.5 years of full protection (1 year in 100% of baseline protection (0.80/0.80) and 1 year in 50% baseline protection (0.40/0.80). Years of full protection can be seen as a single measure that summarizes the waning of the vaccine protection.

Expected vaccine protection over time supplements the *years of full protection* by the duration of the vaccine protection. It is calculated as the sum of the vaccine effectiveness over time. From the above example (VE 0.80 in the first year and 0.40 in the second year) we would calculate 1.2 years as the average duration of protection. The average duration of protection corresponds to the area under the curve of vaccine effectiveness over time.

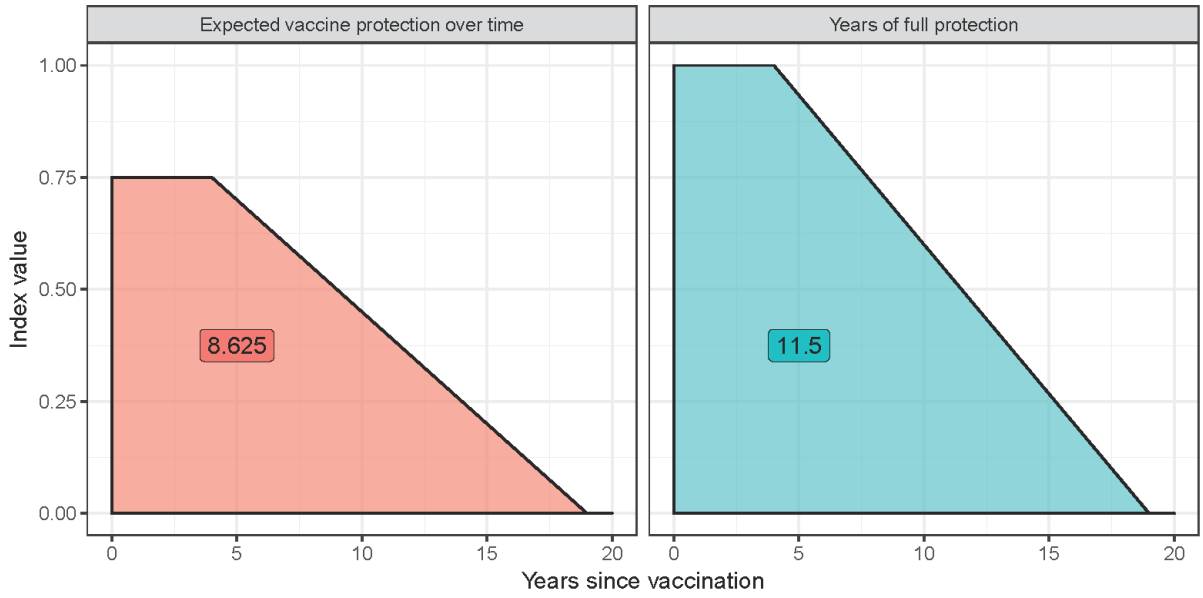

Figure 1: Comparison of the two indices for the measurement of vaccine effectiveness, Years of Full Protection and Expected vaccine protection over time.

Figure 1 compares the two indices on an example, where the VE is constant at maximum level of 75% over 4 years after the vaccination and then decreases linearly over 15 years, reaching 0% in 19 years after the vaccination. The expected vaccine protection over time would be 8.625 *efficacy adjusted protection years* while we would calculate 11.5 years of full protection.

For the studies where the waning lasted over 20 years after the period of the stable protection, in the calculation of EVPOT we stopped the projection on year 20 after the vaccine reception.

It has to be noted that these estimators are biased to some extend because the form of the waning function has an impact on the results of the disease incidence when it is changing with age and/or time. It also has an impact on the economic results when discounting is applied. However, it is still a good metric to compare the assumed effects of vaccination including MVE and waning.

1.1.3. Calculation of age group specific initial vaccine effectiveness based on vaccine-age interaction effects:

To compare the applied effects of vaccination across studies, we reported the initial VE and EVPOT for four age groups: 50-64 years old, 65-74 years old, 75-84 years old and 85+ years. For studies which applied vaccine-age interaction effects [1–6], age group specific VE estimates were calculated as follows:

1. Age specific age VE estimates were calculated based on applied vaccine-age interaction effects and specific VE/age anchor points (for instance PCV13 VE against VT-IPD of 89.2% in 65 years old and vaccine-age interaction effect of 7.8% per year of age).

2. An unweighted average was calculated for each age group based on the age specific vaccine estimates.

Willem et al. [2] did not provide a VE/age anchor point, so that age specific PCV13 VE estimates could not be calculated. Therefore, the reported age independent base VE for IPD and NBPP was used in the comparison of vaccine effects.

For Kuchenbecker et al. [1], age specific VE estimates were calculated based on the linear interpolation technique described in the supplements of the paper.

Kuchenbecker et al. [1] is the only study that applied age specific waning patterns based on linear interpolations of VE against IPD since time of vaccination assumed by Smith et al. 2008 [11] for 50, 65 and 80 years old. Kuchenbecker et al. describe the interpolation technique in detail in the supplements. However, calculated values differ substantially from values reported in the paper. Therefore, we linearly interpolated values reported in the paper. Therefore, our calculation of waning patterns (shown in Figure 3 of our paper) and calculated EVPOTs may differ from the original values applied by Kuchenbecker et al. [1]

1.2. Incidence of vaccine-type pneumococcal disease over time

Observed vaccine-type disease incidence varies across countries and risk groups due to the differences in the overall disease incidence and/or serotype distribution. For the application of vaccine-type disease effectiveness, estimates of vaccine-type disease incidence are required. While this data usually exist for IPD, there is little information on the serotype distribution in non-invasive pneumococcal disease. While there are differences in the distribution between IPD and non-invasive pneumococcal diseases, the assumption of comparable serotype distribution is likely less biased and more transparent in the absence of data than using overall incidence data and estimates of effectiveness against non-invasive pneumococcal disease of any serotype (see arguments in section vaccine-type specific effectiveness).

1.2.1. Indirect herd effect and replacement effects

The observed magnitude of the vaccine induced indirect herd effects and replacement disease differ across countries. The main drivers are the implemented vaccine type for the immunization of infants (PCV7, PCV10 or PCV13) and the vaccination uptake. However, the serotype distribution before the implementation of PCV infant vaccination may also impact the magnitude of effects

The time since the implementation of the infant vaccination program is a crucial factor for the performance and cost-effectiveness of adult vaccination programs. In order to avoid drawing the wrong conclusions on the mid-term performance and cost-effectiveness of adult vaccination, a multi-cohort approach is required.

If the prevention of nasopharyngeal carriage is indeed the cause for the indirect effects on the incidence among the adults, the effects on specific serotypes should at least not completely differ between invasive and non-invasive diseases because the reduced carriage should lead to a decrease in IPD as well as non-IPD cases. However, the indirect effects can differ between the serotypes and the distribution of serotypes may differ

between IPD and non-IPD. These differences may result in varying effects if these serotypes are combined in groups. Van Werkhoven et al. [7] reported that indirect effects of the PCV7 serotypes in IPD and non-invasive disease are comparable. In addition, Rodrigo et al. [8] reported a very low proportion/incidence of PCV7 serotypes after several years of infant vaccination and a decline of the additional PCV13 serotypes in non-IPD after introduction of the PCV13 infant vaccination. In contrast, another US study [9] reported a relatively high burden of PCV7 serotypes in non-invasive pneumonia ten years after the implementation of PCV7 infant vaccination.

For non-invasive disease, in the absence of data, we consider the extrapolation of the effects in IPD the most appropriate method. Using reductions in all-serotype pneumococcal diseases or all-cause non-invasive pneumonia incidence as a predictor for effects in vaccine-type non-IPD is not considered as an appropriate method.

1.2.2. Application of effectiveness data against vaccine type pneumococcal disease

Due to a lack of serotype-specific PD data over time, in particular in non-IPD, effectiveness against PD of any serotype is applied in some studies. This serotype non-specific approach is problematic because it is based on the effectiveness against vaccine serotypes and a specific serotype distribution which is then fixed over time. If the parameter value is directly taken from the clinical trial, it includes the specific serotype distribution in the trial population. If the observed serotype distribution in the target population and the effectiveness against vaccine serotypes are used to calculate the effectiveness against PD of any serotype, it includes the serotype distribution at that specific point in time (for instance pre PCV infant vaccination). The effects of the vaccine are then calculated by applying the vaccine effectiveness against any type to changes in the overall PD incidence over time. The serotype distribution in the overall PD incidence, however, is changing over time due to the indirect effects (herd and replacement) of the childhood vaccination. The reduction of vaccine-type serotypes does not only cause a decrease in the overall PD incidence but also the proportion of vaccine-type serotypes in the remaining overall serotype epidemiology. This time varying proportion of the vaccine-preventable serotypes in the overall serotype distribution is not accounted for in the serotype non-specific approach.

Therefore, such approach would lead to considerable underestimation of the herd effect i.e. decrease in incidence of pneumococcal disease caused by serotypes included into the infant conjugate vaccine. Application of vaccine effectiveness against pneumococcal disease of any serotype or all cause disease brings a high risk of bias due to the changing serotype distributions (regional as well as temporal). Application of vaccine effectiveness against any serotype is therefore not a solution to missing data on serotype distribution which is often the case in non-invasive pneumococcal disease. Additional source of potential bias in incidence of non-invasive pneumococcal disease is usually unknown etiology of pneumonia reported in hospital records. Applying vaccine effectiveness for all cause pneumonia fixes the vaccine effectiveness parameter to a specific serotype distribution as well as a specific proportion of disease caused by *S. pneumonia,* which aggravates the underestimation of the herd effect on the incidence of vaccine type of non-invasive pneumococcal pneumonia.

Below we provide a simplified example of how this particular uncertainty can be exploited to improve effects of adult vaccination.

Example:

Indications:

NBP – non-bacteraemic pneumonia

NBPP – non-bacteraemic pneumococcal pneumonia

Assumptions:

- NBP incidence (per 100,000) in 2018: 1%
- NBPP (attributed to *Streptococcus pneumoniae)* in 2018: 20% of NBP
- Proportion of vaccine serotypes in NBPP in 2018: 40%
- Effectiveness against vaccine-type NBPP: 50%
- Decline of overall NBP incidence over the following five years due to infant conjugate pneumococcal : 5%
- No replacement diseases

Calculated:

- Vaccine effectiveness against NBPP: 0.5*0.4=0.2
- Vaccine effectiveness against NBP: 0.5*0.4*0.2=0.04

Calculated parameters	All-cause approach	All-serotype approach	Serotype-specific approach	Comment
Incidence 2018 (per 100,000)	all-cause NBP: 100,000 x 0.01 = 1,000	S.pn. NBPP: 1,000 x 0.2 = 200	PCV13-type NBPP: 200 x 0.4=80	assumptions of the example are applied to calculate initial incidence
Prevented cases in 2018 at the start of the calculations (per 100,000)	1,000*0.04=40 [VE against all-caused NBP = 0.5*0.4*0.2=0.04]	200 x 0.2=40 [VE against NBPP = 0.5*0.4=0.2]	0.5 x 80 = 40 [VE against vaccine-type NBPP = 0.5]	applied VE to the initial incidence in year 1 of the modelling time horizon shows no difference in prevented cases justifying the all-cause and all-serotype approaches
During the modelled 5 years the incidence of all-cause NBP decreased by 5% due to the herd effect of childhood conjugate vaccination: 50 cases less				
Incidence 2023: under the indirect effect (per 100,000)	1,000 x 0.95 = 950 observed decline is 50 cases	200-50=150	80-50=30	We suggest that observed herd effect (reported as percentile decline of all-cause NBP) can occur only due to the serotypes contained in the childhood conjugate vaccine and the observed decline should be attributed to the PCV13 vaccine-type NBPP incidence. Here the decline of 50 cases is applied to each incidence to show the differences in the approaches.
Prevented cases in 2023 due to adult vaccination	0.04 x 950 = 38	0.2 x 150 = 30	0.5 x 30 = 15	Adult vaccination outcomes at the end of the modelling time horizon.

The example shows that after the application of the herd effect in the model the predictions alter leading to underestimation of the herd effects of childhood vaccination in the vaccine-type pneumococcal disease incidence and overestimation of the adult vaccination outcomes vaccine effects.

2. Study selection process

2.1. Search syntax

The present syntax including the planned limits was used for PubMed:

> (technology assessment, biomedical[MESH] OR “technology assessment” OR “health technology assessment” OR HTA OR policy making[MESH] OR
>
> decision making[MESH] OR costs and cost analysis[MESH] OR “Cost Benefit Analysis” OR “Cost Benefit Analyses” OR “Cost Effectiveness Analysis” OR
>
> “Cost Effectiveness Analyses” OR “Cost Utility Analysis” OR “Cost Utility Analyses” OR “Economic Evaluation” OR “Economic Evaluations” OR “cost
>
> minimization” OR “economic impact” OR “economic models”) AND ("Pneumococcal Vaccines"[Mesh] OR pneumococc* AND (vaccin* OR immun*))
>
> AND (elder* OR old* OR adult OR geriatric* OR years).

The publication bibliographies of the retrieved systematic reviews and the articles selected for the full text review were manually screened to search for related articles.

2.2. *Screening of the identified studies*

Two reviewers (MT, SMS) independently performed the screening of the identified titles and abstracts for eligibility following the above described inclusion criteria. In case of any disagreement, a third reviewer (AK) arbitrated in to reach a consensus. We recorded the reasons for exclusion of ineligible studies. After the screening of the abstracts, the same two reviewers performed the full text review of the selected papers to confirm that the articles met the inclusion criteria.

2.2.1. Inclusion criteria

We included studies with full economic evaluations (cost-effectiveness analyses (CEA), cost-utility analyses (CUA), and cost-benefit analyses (CBA)) of adult vaccination programs with PCV13, PPSV23 or a combination of both. Eligible studies had to include a target population comprising of adult individuals over 50 years old (y.o). We restricted the articles to those that had been published during the period from 2006 to present time. We chose 2006 as a start date because it overlapped with the end date of the literature review published by Ogilvie et al in 2009 [10] We restricted the search to the papers published in English. All countries were included.

2.2.2. Exclusion criteria

We excluded public health-, economic- and budget impact analyses (BIA), systematic reviews, editorials, and conference abstracts, studies evaluating pediatric pneumococcal immunization programs and vaccinating adults younger than 50 years old; the studies which evaluated vaccination against pneumococcal diseases in combination with the vaccination against influenza and the studies which did not explicitly state the type of pneumococcal vaccine under evaluation.

2.2.3. Data extraction

For each of the selected for the full review studies, we firstly extracted the following data on study characteristics: authors, title, DOI/ PMID, year of publication, country, type of economic evaluation, model type, modeled population, vaccine for adult vaccination, comparator, vaccination strategy, vaccination coverage, time horizon, considered morbidities, applied parameters of the vaccine effectiveness, sources of the vaccine effectiveness, duration of protection (waning rate), infant vaccination, inclusion of the indirect effects of childhood vaccination, pneumococcal disease incidence and data sources, perspective, vaccine price and reference year, included costs, discount rate, health outcomes, estimated cost-effectiveness ratios, sensitivity analysis results, conclusions and funding sources.

The same two authors analyzed the extracted the data on the vaccine effectiveness against the vaccine-type pneumococcal serotypes (maximal vaccine effectiveness and duration of protection) and the development of the incidence of vaccine-type pneumococcal diseases over time, which included the disease incidence before the implementation of PCV immunization of infants, its indirect herd- and replacement effects. The data on vaccine effectiveness and duration of protection were used to calculate years of full protection and average duration of protection (see section 1.1.2). These summaries enabled a comparison of applied vaccine protection over time between the studies.

References

1. Kuchenbecker U, Chase D, Reichert A, Schiffner-Rohe J, Atwood M. Estimating the cost-effectiveness of a sequential pneumococcal vaccination program for adults in Germany. PLoS ONE. 2018;13:e0197905. doi:10.1371/journal.pone.0197905.
2. Willem L, Blommaert A, Hanquet G, Thiry N, Bilcke J, Theeten H, et al. Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. Hum Vaccin Immunother. 2018:1–12. doi:10.1080/21645515.2018.1428507.
3. Chen C, Wood JG, Beutels P, Menzies R, MacIntyre CR, Dirmesropian S, et al. The role of timeliness in the cost-effectiveness of older adult vaccination: A case study of pneumococcal conjugate vaccine in Australia. Vaccine. 2018;36:1265–71. doi:10.1016/j.vaccine.2018.01.052.
4. Chen C, Beutels P, Newall AT. Evolution over time in the cost-effectiveness of pneumococcal conjugate vaccine (PCV13) in older Australians due to herd protection from infant vaccination. Vaccine. 2018;36:2057–60. doi:10.1016/j.vaccine.2018.03.006.

5. Dirmesropian S, Wood JG, MacIntyre CR, Beutels P, McIntyre P, Menzies R, et al. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) in older Australians. Vaccine. 2017;35:4307–14. doi:10.1016/j.vaccine.2017.06.085.
6. Mangen M-JJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46:1407–16. doi:10.1183/13993003.00325-2015.
7. van Werkhoven CH, Hollingsworth RC, Huijts SM, Bolkenbaas M, Webber C, Patterson S, et al. Pneumococcal conjugate vaccine herd effects on non-invasive pneumococcal pneumonia in elderly. Vaccine. 2016;34:3275–82. doi:10.1016/j.vaccine.2016.05.002.
8. Rodrigo C, Bewick T, Sheppard C, Greenwood S, Mckeever TM, Trotter CL, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015;45:1632–41. doi:10.1183/09031936.00183614.
9. Sherwin RL, Gray S, Alexander R, McGovern PC, Graepel J, Pride MW, et al. Distribution of 13-Valent Pneumococcal Conjugate Vaccine Streptococcus pneumoniae Serotypes in US Adults Aged >=50 Years With Community-Acquired Pneumonia. Journal of Infectious Diseases. 2013;208:1813–20. doi:10.1093/infdis/jit506.
10. Ogilvie I, Khoury AE, Cui Y, Dasbach E, Grabenstein JD, Goetghebeur M. Cost-effectiveness of pneumococcal polysaccharide vaccination in adults: a systematic review of conclusions and assumptions. Vaccine. 2009;27:4891–904. doi:10.1016/j.vaccine.2009.05.061.
11. Smith KJ, Zimmerman RK, Lin CJ, Nowalk MP, Ko F-S, McEllistrem MC, Roberts MS. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine. 2008;26:1420–31. doi:10.1016/j.vaccine.2008.01.007.

S2 Table 1. Summary of the study design and modelling approaches of the studies included into the full text review but excluded from the quality assessment (n=15).

Authors, year, country	**Study details**	**Vaccination strategy: target population, coverage**	**Parameter structure that governs vaccine effects in the target population**		**Selected for assessment of quality of economic evaluation?**
			Vaccine effectiveness (VE) and Expected vaccine protection over time (given in efficacy adjusted protection years)	Effects of a pneumococcal paediatric vaccination on the incidence in the target population, development of incidence over time	
Merito et al, 2007, Lazio, Italy(Merito et al. 2007)	*Analysis:* CEA of PPSV23 ag. IPD vs no vaccination *Perspective:* public health service *Time horizon:* 5 years *Model type:* Markov, single cohort *Health Outcomes:* LYG *Vaccine price, year:* €12.28, 2004 *Discount*: Cost: 3%;Outcomes: no *Conclusion*: can be cost-effective, great variability of estimates	≥65 y.o, 100%	*Source of VE:* refers to Shapiro et al.(Shapiro et al. 1991), hospital-based case-control study *Parameter:* age-dependent, 65–74y.o: 80%| 75–84y.o: 67%|> 85y.o: 46% *Waning:* at rate after 3 y. *Expected vaccine protection over time:* 65–74y.o: 3.8 | 75–84y.o: 3 | > 85y.o: 1.8	*Paediatric vaccination:* PCV7 or PCV13 not included *Indirect effects:* not included *Methods:* n/a	No. No childhood vaccination program
Rozenbaum et al, 2010, Netherlands(Rozenbaum et al. 2010)	*Analysis:* CEA of PCV13 ag. IPD and nIPD vs no vaccination *Perspective:* societal *Time horizon:* 5 years *Model type:* decision tree, single cohort *Health Outcomes:* LYG *Vaccine price, year:* €50, assumption *Discount*: *Cost*:4%; *Outcomes*:1.5% *Conclusion*: might be considered cost-effective	≥65 y. o; 83% - high-risk; 65% - low-risk	*Source of VE:* assumption *Parameter:* 60% ag. IPD and nIPD, range 30-90% *Waning:* 5 y. stable, waning is not stated *Expected vaccine protection over time:* *3 y.*	*Paediatric vaccination:* PCV7 *Indirect effects:* scenarios: no indirect effects; pessimistic – 100% increase in non-PCV7 serotype incidence *Methods:* assumptions	No. VE of PCV13 is not based on CAPITA and indirect effects are modelled based on assumptions.
Akin et al, 2011, Turkey(Akin et al. 2011)	*Analysis:* CEA of PPSV23 ag. IPD and nIPD vs no vaccination *Perspective:* public payer *Time horizon:* 5 years *Model type:* decision tree, single cohort *Health Outcomes:* LYG *Vaccine price, year:* €16,2008 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: cost-saving	at-risk adults 18-59 y.o40%; ≥60 y.o, 60%	*Source of VE:* assumption based on several observation studies *Parameter:* IPD – 60%, nIPD – 21% *Waning:*10% annual decrease over 5 y. *Expected vaccine protection over time:* IPD-2.5y., nIPD-0.86y	*Paediatric vaccination:* PCV7 not included *Indirect effects:* not included *Methods:* n/a	No. Indirect effects are not applied
Neto et al, 2011, Brazil(Neto et al. 2011)	*Analysis:* CEA of PPSV23 ag. IPD and nIPD vs no vaccination *Perspective:* social, public healthcare *Time horizon:* 5 years *Model type:* decision tree, single cohort *Health Outcomes:* LYG *Vaccine price, year:* US$15, 2008 *Discount*: *Cost*: 5%; *Outcomes*: 5% *Conclusion*: clinically and economically	≥60 y.o, 60%	*Source of VE:* assumption based on several observation studies *Parameter:* IPD – 64%, nIPD – 21% *Waning:*10% annual decrease over 5 y. *Expected vaccine protection over time:* IPD-2.62y., nIPD-0.86y	*Paediatric vaccination:* PCV10 *Indirect effects:* not included *Methods:* n/a	No. Indirect effects are not applied

	favoured				
Grzesiowski et al, 2012, Poland (Grzesiowski et al. 2012)	*Analysis:* CEA of PPSV23 ag. IPD and nIPD vs no vaccination *Perspective:* public health care *Time horizon:* 35 years, lifetime horizon *Model type:* Markov, 10 cohorts *Health Outcomes:* QALY *Vaccine price, year:* not given, 2009 *Discount*: *Cost*: 5%; *Outcomes*:5% *Conclusion*: cost-effective regardless of risk status	strategies: all individuals ≥65 years old; high-risk individuals ≥65 years old; coverage is not stated	*Source of VE:* assumption based on several observation studies *Parameter:* IPD – 64%, nIPD – 21% *Waning:* peak at the 1st year, waning to y. 9. Refers to Sisk et al(Sisk et al. 2003) and Middleton et al (Middleton et al. 2008) *Expected vaccine protection over time:* cannot calculate	*Paediatric vaccination:*PCV7 *Indirect effects*: not in base case, included in SA *Methods:* applied based on epidemiological data of USA and Germany	No. Indirect effects are not included into base case analysis
Kuhlmann et al, 2012, Germany(Kuhlmann et al. 2012)	*Analysis:* CEA, CBA of PPSV23, PCV13 ag. IPD and nIPD vs no vaccination *Perspective:* Statutory Health Insurance *Time horizon:* 100y *Model type:* cross-sectional steady state Markov *Health Outcomes:* LYG *Vaccine price, year:* PCV13: €71.57, PPSV23: €35.89, 2010 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: PCV13 is cost-effective vs PPSV23 and no vaccination, dominates both strategies	*PPSV23:* ≥60 y.o; all patients >5 y.o at high risk + booster +revaccination at 50 with PCV13 *PCV13*: ≥ 50 y.o and the adults at risk + booster for every patient at risk and every second without any risk. Coverage: at risk: 40% other: 25%	*Source of VE:* PCV13: assumption is based on clinical data for PCV7 in children, expecting similar levels of efficacy against the additional 6 serotypes which are not included in PCV7, refer to Black et al (Black et al. 2000). PPSV23: Cochrane systematic literature review(Moberley et al. 2008) *Parameter:* *PCV13 ag.IPD*: 50-59y.o:59.5%|60-69y.o: 60%|70-79y.o:67%|80-89y.o:70.2%| >=90y.o:71.6% *PCV13 ag.* CAPin : 26%|CAPout:6% *PPSV23 ag.IPD*: 50-59y.o:58.4%|60-69 y.o:61.9%|70-79y.o:57.9%|80-89y.o :62.5%|>=90y.o:67% *Waning:* assumed years of full protection and complete waning afterwards PCV13: 10 y. PCV13: 5y. *Expected vaccine protection over time:* cannot calculate	*Paediatric vaccination:* PCV7 *Indirect effects:* applied herd effects *Methods:* as a factor for correction of indirect (herd) effects based on US data adjusted for German serotype coverage.	No. VE of PCV13 is not based on CAPITA
Smith et al, 2012, USA(Smith et al. 2012)	*Analysis:* CEA of PCV13 ag. IPD and nIPD vs no vaccination and current practice with PPSV23 *Perspective:* societal *Time horizon:* lifetime *Model type:* Markov state-transition model *Health Outcomes:* QALY *Vaccine price, year:* PPSV23 $43, PCV13 $128, 2006 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: PCV13 vaccination was favoured compared to PPSV23	strategies: - PCV13 in current ACIP* recommendations - PCV13 at 50y.o + PPSV23 65y.o - PCV13 at ages 50 and 65 - PCV13 at ages 50 and 65, then PPSV23 at age 75. Coverage: 60.1% age-based; 33.9% comorbidity-based	*Source of VE:* estimates of a Delphi expert panel *Parameter:* age, risk dependent PCV13 ag IPD: 50y.o: 90%|65y.o:85% Immunocompromised (all ages): 50% PCV13 ag.nIPD:50y.o: 74%|65y.o:64% Immunocompromised (all ages): 35% PPSV23: 50y.o: 93%|65y.o:85%|80y.o:67% Immunocompromised (all ages): 0% *Waning:* age dependent VE by years since vaccination PCV13 - over 15 y., PPSV23 – over 10 y. *Expected vaccine protection over time (healthy):* PCV13 ag. IPD: 50y.o: 9.6y.| 65y.o:8.1y PCV13 ag. nIPD: 50y.o: 8y.|65y.o:7.3y PPSV23 ag. IPD: 50y.o: 8.1y.|65y.o:5.2y.| 80y.o:3.2y.	*Paediatric vaccination:* PCV13 *Indirect effects:* applied herd immunity *Methods:* extrapolated based on observed age-related PCV7 effects (except serotypes 1 and 5). Potential indirect PCV13 effects for NPP were modelled using point estimates for decreases observed after PCV7 introduction.	No. VE of PCV13 is not based on CAPITA
Weycker et al, USA, 2012 (Weycker et al. 2012)	*Analysis:* CEA od PCV13 ag. IPD and nIPD vs no vaccination, current vaccination program with PPSV23 *Perspective:* healthcare *Time horizon:* lifetime *Model type:* microsimulation framework and a	≥50 y.o -PCV13, with and without periodic revaccination -PPSV23 per current ACIP	*Source of VE:* PCV13 - assumed based on observed PCV7 data in children. Refer to Black et al (Black et al. 2000) PPSV23 – Delphi expert panel. Refer to Smith et al, 2008(Smith et al. 2008) *Parameter:*	*Paediatric vaccination:*PCV13 *Indirect effects:* applied herd immunity *Methods:* assumption	No. VE of PCV13 is not based on CAPITA

	Markov type process *Health Outcomes:* disease-related cases, deaths *Vaccine price, year:* PPSV23 $49, PCV13 $108 2010 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: routine use of PCV13 – in lieu of PPSV23 – would result in a greater reduction in the overall burden of pneumococcal disease	recommendations. Coverage varies by age, risk profile, and vaccination history	Varies for low and high risk groups; and for those with NBP requiring inpatient and outpatient care. Here are the values for low risk group: PCV13 ag IPD: 50-64y.o: 90%|65-74y.o:85% 75-84y.o:80%|>85y.o:73% PCV13 ag NBP inpatient: 50-64y.o:25%|65-74y.o:24%|75-84y.o:23%|>85y.o:22% PPSV23 ag. IPD: 50-64y.o: 83%| 65-74y.o:77%|75-84y.o:68%|>85y.o:57% *Waning:* efficacy by years since vaccination, PCV13 - over 15 y., PPSV23 – over 10 y. *Expected vaccine protection over time:* PCV13 ag IPD: 50-64y.o: 8.2y.|65-74y.o:6.8y. 75-84y.o:5.5y.|>85y.o:3.4y. PCV13 ag NBP inpatient: 50-64y.o: 2.3y|65-74y.o:2.3y|75-84y.o:1.8y|>85y.o:1.5y		
Zhao et al, 2016, Shanghai, China (Zhao et al. 2016)	*Analysis:* CEA of PPSV23 ag IPD vs no vaccination *Perspective:* societal *Time horizon:* lifetime *Model type:* static cohort *Health Outcomes:* QALY, LYG *Vaccine price, year:* PPSV23 - $23.2, 2015 *Discount*: *Cost*: 5%; *Outcomes*:5% *Conclusion*: is cost-effective	≥60 y.o, 63%	*Source of VE:* systematic review and meta-analysis (Kraicer-Melamed et al. 2016; Diao et al. 2016) *Parameter:* PPSV23 ag IPD: 50%, ag nIPD: 0% *Waning:* given as % of initial VE by years since vaccination, waning to 0% by year 9; refer to (Jiang et al. 2012) *Expected vaccine protection over time:* PPSV23 ag IPD: 2.2y	*Paediatric vaccination*: no vaccination of children according to the current data (International Vaccine Access Center) *Indirect effects:* n/a *Methods:* n/a	No. No childhood vaccination program
Smith et al, 2013, USA(Smith et al. 2013)	*Analysis:* CEA of PCV13, PPSV23, combination ag IPD and nIPD vs no vaccination *Perspective:* societal *Time horizon:* lifetime *Model type:* Markov state-transition model *Health Outcomes:* QALY *Vaccine price, year: :* PPSV23 $43, PCV13 $128, 2006 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: single-dose PCV13 strategies are likely to be economically reasonable in older adults	Strategies: Cohort 65 y.o -15 strategies; Cohort 75y.o -7 strategies, include different age of administration, PCV13 and PPSV23 alone and in combination	*Source of VE:* Delphi expert panel *Parameter:* age, risk dependent PCV13 ag IPD: 65y.o: 85%|75y.o:79% Immunocompromised (all ages): 50% PCV13 ag nIPD: 65y.o: 64%|75y.o:59% Immunocompromised (all ages): 35% PPSV23 ag IPD: 65y.o: 80%|80y.o:67% Immunocompromised (all ages): 0% *Waning:* age dependent VE by years since start PCV13 - over 15 y., PPSV23 – over 7 y. *Expected vaccine protection over time (healthy):* PCV13 ag IPD:65-75y.o:9.6y.|>=75y.o:8y PCV13 ag nIPD: 65-75y.o:7.3y.|>=75y.o:6y PPSV23 ag IPD: 65-80y.o:5.2y.|>=80y.o:3.4y	*Paediatric vaccination:* PCV13 *Indirect effects:* herd immunity and serotype replacement *Methods:* projections of PCV7 effects	No.VE of PCV13 is not based on CAPITA
Chen et al, 2014, USA (Chen et al. 2014)	*Analysis:* CEA of PCV13, combination with PPSV23 ag IPD and nIPD vs no vaccination *Perspective:* payer *Time horizon:* lifetime *Model type:* static single cohort *Health Outcomes:* QALY *Vaccine price, year:* PCV13 $120.95, PPSV23 $57.70, administration - $15.00 ,*2012* *Discount*: *Cost*: 3%; *Outcomes*:3%	≥50 y.o, 7 strategies. 2012 ACIP recommendations** Coverage differs across age- and risk subgroups ranges 7-57.1%,	*Source of VE:* estimates by a Delphi expert panel *Parameter:* PCV13 ag IPD: Healthy: 50y.o:80%|65y.o:72.5% Immunocompetent with comorbidities: 50y.o:67.5%|65y.o:61.2% Immunocompromised: 50y.o:53%|65y.o:48% PCV13 ag nIPD: Healthy: 50y.o:68%|65y.o:60.5%	*Paediatric vaccination:* PCV13 *Indirect effects:* non in base case, applied in SA herd immunity and replacement *Methods:* projections of observed PCV7 effects, three sets of assumptions	No. VE of PCV13 is not based on CAPITA; indirect effects are applied in SA

	Conclusion: additional dose of PCV13 at age 65, followed by PPSV23, for adults with immunocompromising conditions is cost-effective		Immunocompetent with comorbidities: 50y.o:56%|65y.o:49.8% Immunocompromised: 50y.o:7%|65y.o:6.2% PPSV23 ag IPD: Healthy: 50y.o:82.7%|65y.o:73.7% Immunocompetent with comorbidities: 50y.o:70.3%|65y.o:62.7% Immunocompromised: 50y.o:18%|65y.o:16.1% PPSV23 ag nIPD: Healthy: 50y.o:49.5%|65y.o:36.5% Immunocompetent with comorbidities: 50y.o:36.5%|65y.o:26.9% Immunocompromised: 0% *Waning:* assumed linear waning, PCV13 over 15y., PPSV23 over 10y. *Expected vaccine protection over time:* cannot calculate		
Liguori et al, 2014, Campania, Italy(Liguori et al. 2014)	*Analysis:* BIA,CEA of PCV13 ag pneumococcal pneumonia (PP) vs no vaccination *Perspective:* National Health Service *Time horizon:* 5 years *Model type:* economic model *Health Outcomes:* disease-related cases *Vaccine price, year:* €42.5, not stated *Discount*: *Cost*: 3%; *Outcomes*: none *Conclusion*: both hypothesized immunization strategies could produce savings	2 scenarios - high risk people of 50-79 years old - high risk people of 50-64 years old and people ≥65 years old Coverage: 60%	*Source of VE:* previously published studies *Parameter:* PCV13 ag PP: 87.5% *Waning:* not stated. The study does not provide in detail information about the input parameters. It may be assumed that the VE of PCV13 was applied for 5 years of full protection. *Expected vaccine protection over time:* n/a	*Paediatric vaccination:* PCV13 *Indirect effects:* the authors do not mention the paediatric vaccination *Methods:* n/a	No VE of PCV13 is not based on CAPITA; indirect effects are not applied
Ordóñez, Orozco, 2014, Colombia(Ordonez and Orozco 2014)	*Analysis:* CEA of PCV13 ag IPD and nIPD vs no vaccination and PPSV23. *Perspective:* third party payer *Time horizon:* 5 years *Model type:* Markov microsimulation model *Health Outcomes:* disease-related cases, deaths *Vaccine price, year:* PCV13 U.S.$ 15.84, PPSV23 U.S.$6.60, 2013 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: cost-saving strategy	individuals ≥50 y.o, 70%	*Source of VE:* PCV13 - adapted from VE of PCV7 for children with assumption: similar VE ag. 6 serotypes not included in PCV7. Refer to (Black et al. 2000),(Hansen et al. 2006) PPSV23 - estimates of Delphi expert panel. Refer to Smith,2008 (Smith et al. 2008), Shapiro et al(Shapiro et al. 1991) *Parameter:* PCV13 ag IPD: 50-64y.o:88.9%|65-74y.o:81.5% 75-79y.o:75.7%|80-99y.o:70.3% PCV13 ag CAP-inpatient/CAP-outpatient 50-64y.o:24.2%; 5.6%|65-74y.o:21.9%/5.1%| 75-79y.o:20.2%/4.7%|80-99y.o:18.7%/4.3% PPSV23 ag IPD: 50-64y.o:79.2%|65-74y.o:61.6% 75-79y.o:50.4%|80-99y.o:42.1% *Waning:* not explicitly given, assumed rate of decline, for PPSV23 refer to (Alonso-Fernández and La Fuente 2011), for PCV13- decline assumed as 50% of the corresponding rate of decline for PPSV23. *Expected vaccine protection over time:* cannot calculate	*Paediatric vaccination:* PCV10 *Indirect effects:* the authors do not mention the paediatric vaccination *Methods:* n/a	No. VE of PCV13 is not based on CAPITA; indirect effects are not applied

Soarez et al, 2015, Brazil (Soarez et al. 2015)	*Analysis:* CEA of universal PPSV23 vaccination ag IPD and nIPD vs vaccination of institutionalized elderly and elderly with underlying diseases *Perspective:* health system, societal *Time horizon:*10 years *Model type:* Markov, single cohort *Health Outcomes:* life years saved (LYS) *Vaccine price, year:* USD$6.25, not stated *Discount*: *Cost*: 5%; *Outcomes*:5% *Conclusion*: universal vaccination with PPSV23 is very cost-effective	≥50 y.o, single dose, 80%	*Source of VE:* ag IPD: a meta-analysis of 18 randomized control trials and 7 non randomized studies (Moberley et al. 2013); ag nIPD: observational studies (Ochoa-Gondar et al. 2014; Vila-Córcoles et al. 2006) *Parameter:* PPSV23 ag IPD: 68%; ag nIPD: all cause Pn: 25%; NBPP: 45% *Waning:* protection ag IPD: 3rd - 5th year: 6.8% 6th-10th year: 8.5% waning Protection ag nIPD: full for 5 years. *Expected vaccine protection over time:* ag IPD: 5.8y.; ag nIPD: 1.25y.	*Paediatric vaccination:* PCV10 *Indirect effects:* not included *Methods:* n/a	No. Indirect effects are not applied
Hoshi et al, 2015, Japan (Hoshi et al. 2015)	*Analysis:* CEA of PPSV23, PCV13 ag IPD and nIPD vs current vaccination with PPSV23, no vaccination *Perspective:* payers' *Time horizon:* 15 years *Model type:* Markov *Health Outcomes:* QALY *Vaccine price, year:* PPSV23- US$43, PCV13 - US$65, 2014 *Discount*: *Cost*: 3%; *Outcomes*:3% *Conclusion*: scenarios with different levels of share of PCV13 have favourable ICERs but were not cost-saving compared to current strategy; ≥65 PPSV23 strategy or including PCV13 has value for money	Strategies: PPSV23: 60-85 year olds, ≥65 year olds, singles dose. PCV13: replacement of PPSV23, single dose. 10 scenarios with varying PCV13 diffusion levels. Coverage for all 50.4%	*Source of VE:* based on 3 sources: Smith et al (2012),(Smith et al. 2012) for both vaccines; Cochrane literature review(Moberley et al. 2013) for PPSV23; CAPITA study for PCV13(Bonten et al. 2015) *Parameter:* PCV13 ag IPD: 65-79y.o:75%|≥80y.o:62.8% PCV13 ag nIPD: 65-79y.o:45%|≥80y.o:37.7% PPSV23 ag IPD:65-79y.o:82%|≥80y.o:68.7% PPSV23 ag nIPD:0% *Waning:* PCV13 over 15y., PPSV23 over 7y. VE by years since vaccination, age-dependent. *Expected vaccine protection over time:* PCV13 ag IPD: 65-79y.o:7.1y|≥80y.o:3.4y PCV13 ag nIPD: 65-79y.o:4.9y|≥80y.o:2.1y PPSV23 ag IPD: 65-79y.o:5.3y|≥80y.o:3.4y	*Paediatric vaccination:* PCV7, PCV13 *Indirect effects:* indirect effects not included because of "fear of bias" *Methods:* n/a	No. Indirect effects are not applied

Abbreviations: ACIP the Advisory Committee on Immunization Practices; CAP -community-acquired pneumonia; CEA - cost-effectiveness analysis; LYG - life years gained; n/a – not applicable; nIPD – non-invasive pneumococcal diseases; PD - pneumococcal disease; Pn - pneumonia; SA - sensitivity analyses; STIKO - the German standing committee for vaccination; VE- vaccine effectiveness; y.- years; y.o - years old

* ACIP at the time of the study: vaccinate all persons with PPSV23 at age 65; those who received PPSV23 before age 65 for a comorbid condition are recommended to receive another dose at age 65 or later if at least 5 years have passed since the previous dose

**ACIP,2012 - to include a sequential regimen of 13-valent pneumococcal conjugate vaccine (PCV13) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) for certain high-risk adults with immunocompromising conditions (Chen et al. 2014).

Publication bibliography

Akin, Levent; Kaya, Mehmet; Altinel, Serdar; Durand, Laure (2011): Cost of pneumococcal infections and cost-effectiveness analysis of pneumococcal vaccination at risk adults and elderly in Turkey. In *Human vaccines* 7 (4), pp. 441–450.

Alonso-Fernández, Patricia; La Fuente, Mónica de (2011): Role of the immune system in aging and longevity. In *Current aging science* 4 (2), pp. 78–100.

Black, S.; Shinefield, H.; Fireman, B.; Lewis, E.; Ray, P.; Hansen, J. R. et al. (2000): Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. In *The Pediatric infectious disease journal* 19 (3), pp. 187–195.

Bonten, Marc J. M.; Huijts, Susanne M.; Bolkenbaas, Marieke; Webber, Chris; Patterson, Scott; Gault, Samantha et al. (2015): Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. In *The New England journal of medicine* 372 (12), pp. 1114–1125. DOI: 10.1056/NEJMoa1408544.

Chen, Jieling; O'Brien, Megan A.; Yang, H. Keri; Grabenstein, John D.; Dasbach, Erik J. (2014): Cost-effectiveness of pneumococcal vaccines for adults in the United States. In *Advances in therapy* 31 (4), pp. 392–409. DOI: 10.1007/s12325-014-0115-y.

Diao, Wen-Qi; Shen, Ning; Yu, Pan-Xi; Liu, Bei-Bei; He, Bei (2016): Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. In *Vaccine* 34 (13), pp. 1496–1503. DOI: 10.1016/j.vaccine.2016.02.023.

Grzesiowski, Pawel; Aguiar-Ibanez, Raquel; Kobryn, Aleksandra; Durand, Laure; Puig, Pierre-Emmanuel (2012): Cost-effectiveness of polysaccharide pneumococcal vaccination in people aged 65 and above in Poland. In *Human vaccines & immunotherapeutics* 8 (10), pp. 1382–1394. DOI: 10.4161/hv.21571.

Hansen, John; Black, Steven; Shinefield, Henry; Cherian, Thomas; Benson, Jane; Fireman, Bruce et al. (2006): Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. In *The Pediatric infectious disease journal* 25 (9), pp. 779–781. DOI: 10.1097/01.inf.0000232706.35674.2f.

Hoshi, Shu-ling; Kondo, Masahide; Okubo, Ichiro (2015): Economic Evaluation of Immunisation Programme of 23-Valent Pneumococcal Polysaccharide Vaccine and the Inclusion of 13-Valent Pneumococcal Conjugate Vaccine in the List for Single-Dose Subsidy to the Elderly in Japan. In *PloS one* 10 (10), e0139140. DOI: 10.1371/journal.pone.0139140.

International Vaccine Access Center: http://view-hub.org/. International Vaccine Access Center. Available online at http://view-hub.org/viz/?YXBwaWQ9MSZpbmRpY2F0b3JpZD01NSZvdmVybGF5aWQ9NA==, checked on 05/30/2018.

Jiang, Yiling; Gauthier, Aline; Annemans, Lieven; van der Linden, Mark; Nicolas-Spony, Laurence; Bresse, Xavier (2012): Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. In *Expert review of pharmacoeconomics & outcomes research* 12 (5), pp. 645–660. DOI: 10.1586/erp.12.54.

Kraicer-Melamed, Hannah; O'Donnell, Shauna; Quach, Caroline (2016): The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. In *Vaccine* 34 (13), pp. 1540–1550. DOI: 10.1016/j.vaccine.2016.02.024.

Kuhlmann, Alexander; Theidel, Ulrike; Pletz, Mathias W.; Schulenburg, J-Matthias Graf von der (2012): Potential cost-effectiveness and benefit-cost ratios of adult pneumococcal vaccination in Germany. In *Health economics review* 2 (1), p. 4. DOI: 10.1186/2191-1991-2-4.

Liguori, Giorgio; Parlato, Antonino; Zamparelli, Alessandro Sanduzzi; Belfiore, Patrizia; Galle, Francesca; Di Onofrio, Valeria et al. (2014): Adult immunization with 13-valent pneumococcal vaccine in Campania region, South Italy: an economic evaluation. In *Human vaccines & immunotherapeutics* 10 (2), pp. 492–497. DOI: 10.4161/hv.26888.

Merito, Monica; Giorgi Rossi, Paolo; Mantovani, Jessica; Curtale, Filippo; Borgia, Piero; Guasticchi, Gabriella (2007): Cost-effectiveness of vaccinating for invasive pneumococcal disease in the elderly in the Lazio region of Italy. In *Vaccine* 25 (3), pp. 458–465. DOI: 10.1016/j.vaccine.2006.08.005.

Middleton, Donald B.; Lin, Chyongchiou J.; Smith, Kenneth J.; Zimmerman, Richard K.; Nowalk, Mary Patricia; Roberts, Mark S.; Fox, Dwight E. (2008): Economic evaluation of standing order programs for pneumococcal vaccination of hospitalized elderly patients. In *Infection control and hospital epidemiology* 29 (5), pp. 385–394. DOI: 10.1086/587155.

Moberley, S. A.; Holden, J.; Tatham, D. P.; Andrews, R. M. (2008): Vaccines for preventing pneumococcal infection in adults. In *The Cochrane database of systematic reviews* (1), CD000422. DOI: 10.1002/14651858.CD000422.pub2.

Moberley, Sarah; Holden, John; Tatham, David Paul; Andrews, Ross M. (2013): Vaccines for preventing pneumococcal infection in adults. In *The Cochrane database of systematic reviews* (1), CD000422. DOI: 10.1002/14651858.CD000422.pub3.

Neto, Joao Tonolio; Araujo, Gabriela Tannus Branco de; Gagliardi, Anna; Pinho, Amanda; Durand, Laure; Fonseca, Marcelo (2011): Cost-effectiveness analysis of pneumococcal polysaccharide vaccination from age 60 in Sao Paulo State, Brazil. In *Human vaccines* 7 (10), pp. 1037–1047. DOI: 10.4161/hv.7.10.15987.

Ochoa-Gondar, Olga; Vila-Corcoles, Angel; Rodriguez-Blanco, Teresa; Gomez-Bertomeu, Frederic; Figuerola-Massana, Enric; Raga-Luria, Xavier; Hospital-Guardiola, Imma (2014): Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged ≥ 60 years: 3 years of follow-up in the CAPAMIS study. In *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 58 (7), pp. 909–917. DOI: 10.1093/cid/ciu002.

Ordonez, Jaime E.; Orozco, John J. (2014): Cost-effectiveness analysis of pneumococcal conjugate vaccine 13-valent in older adults in Colombia. In *BMC infectious diseases* 14, p. 172. DOI: 10.1186/1471-2334-14-172.

Rozenbaum, Mark H.; Hak, Eelko; van der Werf, Tjip S.; Postma, Maarten J. (2010): Results of a cohort model analysis of the cost-effectiveness of routine immunization with 13-valent pneumococcal conjugate vaccine of those aged or =65 years in the Netherlands. In *Clinical therapeutics* 32 (8), pp. 1517–1532. DOI: 10.1016/j.clinthera.2010.06.016.

Shapiro, E. D.; Berg, A. T.; Austrian, R.; Schroeder, D.; Parcells, V.; Margolis, A. et al. (1991): The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. In *The New England journal of medicine* 325 (21), pp. 1453–1460. DOI: 10.1056/NEJM199111213252101.

Sisk, Jane E.; Whang, William; Butler, Jay C.; Sneller, Vishnu-Priya; Whitney, Cynthia G. (2003): Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: role of comorbid conditions and race. In *Annals of internal medicine* 138 (12), pp. 960–968.

Smith, Kenneth J.; Wateska, Angela R.; Nowalk, Mary Patricia; Raymund, Mahlon; Lee, Bruce Y.; Zimmerman, Richard K. (2013): Modeling of cost effectiveness of pneumococcal conjugate vaccination strategies in U.S. older adults. In *American journal of preventive medicine* 44 (4), pp. 373–381. DOI: 10.1016/j.amepre.2012.11.035.

Smith, Kenneth J.; Wateska, Angela R.; Nowalk, Mary Patricia; Raymund, Mahlon; Nuorti, J. Pekka; Zimmerman, Richard K. (2012): Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. In *JAMA* 307 (8), pp. 804–812. DOI: 10.1001/jama.2012.169.

Smith, Kenneth J.; Zimmerman, Richard K.; Lin, Chyongchiou J.; Nowalk, Mary Patricia; Ko, Feng-Shou; McEllistrem, M. Catherine; Roberts, Mark S. (2008): Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. In *Vaccine* 26 (11), pp. 1420–1431. DOI: 10.1016/j.vaccine.2008.01.007.

Soarez, Patricia Coelho de; Sartori, Ana Marli Christovam; Freitas, Angela Carvalho; Nishikawa, Alvaro Mitsunori; Novaes, Hillegonda Maria Dutilh (2015): Cost-Effectiveness Analysis of Universal Vaccination of Adults Aged 60 Years with 23-Valent Pneumococcal Polysaccharide Vaccine versus Current Practice in Brazil. In *PloS one* 10 (6), e0130217. DOI: 10.1371/journal.pone.0130217.

Vila-Córcoles, Angel; Ochoa-Gondar, Olga; Hospital, Imma; Ansa, Xabier; Vilanova, Angels; Rodríguez, Teresa; Llor, Carl (2006): Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. In *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 43 (7), pp. 860–868. DOI: 10.1086/507340.

Weycker, Derek; Sato, Reiko; Strutton, David; Edelsberg, John; Atwood, Mark; Jackson, Lisa A. (2012): Public health and economic impact of 13-valent pneumococcal conjugate vaccine in US adults aged ≥50 years. In *Vaccine* 30 (36), pp. 5437–5444. DOI: 10.1016/j.vaccine.2012.05.076.

Zhao, Daijun; Gai Tobe, Ruoyan; Cui, Min; He, Jinchun; Wu, Bin (2016): Cost-effectiveness of a 23-valent pneumococcal polysaccharide vaccine immunization programme for the elderly in Shanghai, China. In *Vaccine* 34 (50), pp. 6158–6165. DOI: 10.1016/j.vaccine.2016.11.003.

S3: Summaries of the main studies used as sources for the vaccine effectiveness estimates.

Pneumococcal conjugate vaccines.

PCV7

Black et al. 2000: Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. (RCT) [1]

Population	Healthy infants
Intervention	PCV7 vaccinated at 2, 4, 6 and 12 to 15 months
Comparator	meningococcus type C conjugate vaccine
Outcome	Primary: Invasive disease caused by vaccine serotype Secondary: Invasive disease regardless of serotype, effectiveness against clinical otitis media visits and episodes, impact against frequent and severe otitis media and ventilatory tube placement
Setting	23 medical centers within Northern California Kaiser Permanente (NCKP)

The authors present the results of a double blind, randomized trial in which 37,868 children at 2, 4, 6 and 12 to 15 months were assigned to the heptavalent pneumococcal or the meningococcus type C vaccine. Enrollment was between October 1995 and August 1998. The interim analysis was conducted in August 1998 and showed the following results. VE against IPD showed to be 97.4% for per protocol fully vaccinated and 93.9% for the intention to treat population. No age-stratification or information on waning are given.

PCV13

Bonten et al. 2015: Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. (RCT) [2]

Population	Adults 65 years of age or older
Intervention	PCV13 (+ influenza vaccine), one shot
Comparator	Placebo (+ influenza vaccine)
Outcome	first episodes of vaccine-type strains of pneumococcal CAP, nonbacteremic and noninvasive pneumococcal, CAP, IPD
Setting	101 temporary community-based sites throughout the Netherlands

The efficacy of PCV13 was evaluated via a randomized, double-blind, placebo-controlled trial (the CAPITA study) involving 84,496 adults 65 years of age or older for the end-points pneumococcal community-acquired pneumonia (CAP), nonbacteremic and noninvasive pneumococcal community-acquired pneumonia (NCAP), and invasive pneumococcal disease (IPD). The mean follow-up time was 3.97 years for which the VE showed to be 45.6% against CAP, 45.0% against NCAP and 75.0% against IPD for the per protocol analysis and 37.7%, 41.1%% and 75.8% for the intention to treat analysis, respectively. The VE was persistent throughout the duration of the trial.

Frenck et al. 2016: Immunogenicity and safety of a second administration of 13-valent pneumococcal conjugate vaccine 5 years after initial vaccination in adults 50 years and older. (Cohort) [3]

Population	Adults 55 to 65 years of age or older
Intervention	Revaccination with PCV13 (+ influenza vaccine) five years after initial vaccination
Comparator	NA
Outcome	Antipneumococcal polysaccharide opsonophagocytic activity (OPA) geo-metric mean titers (GMTs) and immunoglobulin G (IgG) geometric mean concentrations (GMCs)
Setting	34 sites in the United States

This study reports on the waning antibody titers within five years of the vaccination of 50 to 59 year old (at first vaccination) and the ability of re-vaccination to boost titers. The study reports no patient relevant outcomes besides adverse events. The authors state that "antibody titers were maintained for at least 5 years after vaccination". However, the plots indicate a decline in titers over the five years.

Patterson et al. 2016: A post hoc assessment of duration of protection in CAPITA (Community Acquired Pneumonia immunization Trial in Adults). (RCT) [4]

Population	Adults 65 years of age or older
Intervention	PCV13 (+ influenza vaccine), one shot
Comparator	Placebo (+ influenza vaccine)
Outcome	first episodes of vaccine-type strains of pneumococcal CAP, nonbacteremic and noninvasive pneumococcal, CAP, IPD
Setting	101 temporary community-based sites throughout the Netherlands

This paper presents a re-analysis of the data presented in Bonten et al. 2015 from the CAPITA trial with an emphasis on the duration of protection (i.e., waning). The results show that PCV13 was protective over the 5-year duration of the study, with no waning of efficacy observed. VE against vaccine-type CAP varies between 42.9% and 50.0%, vaccine-type IPD between 66.7% and 75.0% and nonbacteremic/noninvasive-vaccine-type CAP between 36.2% and 48.9% for the first five years after vaccination.

van Werkhoven et al. 2015: The Impact of Age on the Efficacy of 13-valent Pneumococcal Conjugate Vaccine in Elderly. (RCT) [5]

Population	Adults 65 years of age or older
Intervention	PCV13 (+ influenza vaccine), one shot
Comparator	Placebo (+ influenza vaccine)
Outcome	first episodes of vaccine-type strains of pneumococcal CAP, nonbacteremic and noninvasive pneumococcal, CAP, IPD
Setting	101 temporary community-based sites throughout the Netherlands

This paper presents a re-analysis of the data presented in Bonten et al. 2015 from the CAPITA trial with an emphasis on the impact of age on VE. Age-dependent VE was estimated via a Cox proportional hazard model and the results by age are given as graphical representation including a 95% confidence interval based on 2,000 bootstrap samples.

Pneumococcal polysaccharide vaccines.

PPSV23

Andrews et al. 2012: Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. (Case control) [6]

Population	Adults 65 years of age or older
Intervention	PPSV23 (and PCV7 vaccination for children)
Comparator	No vaccination
Outcome	IPD
Setting	England and Wales between 1998/99 and 2009/10

The authors present a combined ecological and case-control study. The ecological study documents the changes in overall and serotype specific incidence of IPD in England and Wales between 1998/99 and 2009/10. The proportion of cases with specified serotypes increased over time from 36% to 83% over the covered period. Stratification by serotype includes the categories "Non23v", "23v", "23v-7v" and "7v". Results on PPSV23 effectiveness against IPD are available for the age groups 65-74, 75-84 and ≥85 years and are given for the time periods <2 years, 2 to <5 years and ≥ 5 years.

Diao et al. 2016: Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. (Meta-analysis) [7]

Population	Immunocompetent adults ≥15 years
Intervention	PPSV23
Comparator	Placebo, influenza vaccine or no intervention
Outcome	all-cause pneumonia, pneumococcal pneumonia, all-cause mortality and mortality due to pneumonia
Setting	worldwide

This study presents the results of a systematic review and meta-analysis on RCTs on the effectiveness of PPSV23 in immunocompetent adults ≥15 years. 7 randomized trials involving 156,010 participants were included in the meta-analysis and found a weak association between PPSV23 vaccination and all-cause pneumonia [RR 0.87, 95%CI 0.76–0.98]. The protective effect was stronger for the target population, defined as adults ≥65 years and patients at high risk for pneumonia, with [RR 0.72, 95%CI 0.69–0.94] and against pneumococcal pneumonia [RR 0.54, 95%CI 0.18–1.65]. No results on vaccine-serotypes, age or time since vaccination (waning) are given.

Falkenhorst et al. 2017: Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. (Meta-Analysis) [8]

Population	Adults 60 years of age or older
Intervention	PPSV23
Comparator	*NA*
Outcome	IPD, pneumococcal pneumonia
Setting	Industrialized countries

This publication presents the results of a systematic literature review and a meta-analysis of the VE of PPSV23 in the elderly, defined as ≥60 years of age, against pneumococcal pneumonia (PP) and invasive pneumococcal disease (IPD). 13 observational studies and four RCTs are included that compare PPSV23 with a "no vaccination" strategy or placebo. For IPD pooled results for all-type IPD showed a VE of 73% in the clinical trials vs. 58% for cohort studies and 59% for case-control studies. Vaccine-type IPD was only reported in two case-control studies (73% VE). For PP pooling resulted in

a VE of 25% in clinical trials, 53% in one case control study an 37% in one case-case study. The results are not available by age or over time.

Gutierrez Rodriguez et al. 2014: Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008–2011. (Cohort) [9]

Population	Adults 60 years of age or older
Intervention	PPSV23 (within and after the fifth year after vaccination)
Comparator	*NA*
Outcome	IPD
Setting	Region of Madrid, Spain, 2008–2011

The study analyzes the IPD incidence in the region of Madrid between 2008 and 2011 of persons 60 years and older and estimates the vaccine effectiveness (VE) via two different approaches, i.e., the screening method and the indirect cohort method. Persons were deemed as "vaccinated" if vaccination happened at least 15 days before the onset of IPD symptoms, but no upper limit on the period since vaccination has been applied. Analysis of VE were stratified by the groups "vaccinated within 5 years" and "vaccinated more than 5 years ago". The unadjusted VE of PPSV23 was estimated to be 40.5% [95%CI 28.3%-59.4%] and increased to 72.8% [95%CI 59.1%-81.8%] in the adjusted analysis. The unadjusted VE varies by the time since vaccination with 44.5% if persons were vaccinated within the previous five years and 32.5% if the vaccine had been administered more than five years.

Huss et al. 2009: Efficacy of pneumococcal vaccination in adults: a meta-analysis. (Meta-analysis) [10]

Population	Adults (no age boundary given)
Intervention	PPSV
Comparator	Placebo, other vaccines or no intervention
Outcome	(a) definitive pneumococcal pneumonia, defined as typical clinical or radiologic findings and S. pneumoniae isolated from normally sterile body fluid such as blood; (b) presumptive pneumococcal pneumonia, defined as typical clinical or radiologic findings, and either S. pneumoniae isolated from respiratory tract samples or seroconversion against S. pneumoniae; (c) pneumonia from all causes; (d) bronchitis from all causes; (e) death from all causes; (f) death from pneumonia; (g) death from pneumococcal infection; and (h) bacteremia or invasive pneumococcal disease, defined as S. pneumoniae isolated from a usually sterile body fluid such as blood
Setting	worldwide

This meta-analysis includes 22 studies to pool the evidence on the effectiveness of PPSV vaccines, with 8 trials reporting findings on the 23 valent vaccine. The authors found the vaccines to be more effective on definitive pneumococcal pneumonia (RR0.62, 95%CI 0.05–8.61) than on all-cause pneumonia (RR0.73, 95%CI 0.56–0.94). The protective effect on bacteremia was not significant (RR0.90, 95%CI 0.46–1.77) which they also found for death from pneumococcal infections (RR0.93, 95%CI 0.29–3.05). No stratification according to the valency of the vaccine, age group or time since vaccination (waning) is provided.

Kraicer-Melamed et al. 2016: The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. (Meta-analysis) [11]

Population	Adults 50 years of age or older, no underlying medical conditions leading to immune suppression

Intervention	PPSV23
Comparator	*NA*
Outcome	IPD, pneumococcal pneumonia
Setting	General population (i.e., no nursing home residents)

This paper presents the results of a systematic review and meta-analysis of the PPSV23 VE in persons 50 years and older against IPD and CAP. 32 studies have finally been included in the analyses with 12 studies reporting only on IPD and 12 only on CAP. 3 publications were reporting results from trials, 11 cohort studies, 10 case control studies, 3 ecological studies and 5 studies using data from surveillance systems. The pooled VEs were 50% (95%CI 21–69%) for cohort studies and 54% (95%CI 32–69%) for case–control studies against IPD, and 4% (95%CI -26% to 26%) for trials, 17% (95%CI −26% to 45%) for cohort studies, and 7% (95%CI -10% to 21%) for case–control studies against CAP. No further stratification of the results can be found.

Middleton et al. 2008: Economic Evaluation of Standing Order Programs for Pneumococcal Vaccination of Hospitalized Elderly Patients. (Economic Evaluation) [12]

Population	Hospitalized adults 65 years of age or older
Intervention	PPSV23 vaccination according to SOP
Comparator	PPSV23 vaccination without SOP
Outcome	Vaccination rates, cost-effectiveness
Setting	The University of Pittsburgh Medical Center Health System

This study is a cost-effectiveness analysis using data on VE from another cost-effectiveness study (Weaver et al. 2001) that uses data from Shapiro et al. 1991 in the form as reported by another cost-effectiveness study (Sisk et al. 1997).

Ochoa-Gondar et al. 2014: Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine Against Community-Acquired Pneumonia in the General Population Aged ≥60 Years: 3 Years of Follow-up in the CAPAMIS Study. (Cohort) [13]

Population	Adults 60 years of age or older
Intervention	PPSV23
Comparator	*NA*
Outcome	bacteremic pneumococcal CAP nonbacteremic pneumococcal CAP all-cause CAP
Setting	General population in Tarragona, Spain

This paper presents the results of a population-based cohort study including 27,204 persons 60 years and older between 2008 and 2011 which evaluates the effectiveness of PPSV23 against pneumococcal and all-cause CAP, respectively. Comparing vaccinated with un-vaccinated persons revealed no significant protective effect of PPSV against bacteremic pneumococcal CAP, nonbacteremic pneumococcal CAP, all-cause CAP or mortality, even when adjusting for available co-variates. Only considering persons vaccinated during the study period showed a protective, significant effect of the vaccine agains pneumococcal CAP (hazard ratio 0.09).

Shapiro et al. 1991: The protective efficacy of polyvalent pneumoccal polysaccharide vaccine. (Case control) [14]

Population	Adults 60 years of age or older
Intervention	PPSV23 and PPSV14

Comparator	No vaccination
Outcome	S. pneumonia infections as confirmed isolations
Setting	11 large hospitals in Connecticut, USA

The authors present the results of a case control study analyzing the effectiveness of the 14-valent and the 23-valent vaccine. From 1,054 cases with isolated *S. pneumoniae* 137 had received a vaccine compared to 211 vaccinated persons of 1,054 controls. 191 cases were categorized as immune-compromised. The VE against vaccine-serotypes, calculated as 1 minus odds ratio of being vaccinated divided by 100, was 56% [95%CI 42%-67%]. VE was higher for immune-competent patients with 61% [95%CI 47%-72%]. Results for immune-competent patients are further stratified by age groups (<55, 55-64, 65-74, 75-84, ≥85) and time since vaccination (<3 years, 3-5 years, >5 years). VE decreases with age and time since vaccination.

Smith et al. 2008: Alternative strategies for adult pneumococcal polysaccharide vaccination: A cost-effectiveness analysis (Economic evaluation) [15]

Population	Adults 50 years of age or older
Intervention	Different strategies of PPSV23 vaccination
Comparator	No vaccination
Outcome	Cost-effectiveness
Setting	USA

This study presents the results of a cost-effectiveness analysis on different vaccination strategies using PPSV23. The VE is estimated via a Delphi expert panel that used the data of Shapiro et al. 1991 as basis for the expert estimates. Values are estimated for healthy persons in three age groups (50 years, 65 years and 80 years) and for immunocompromised of all ages, each for different time points after vaccination (1, 3, 5, 7, 10 and 15 years).

Smith et al. 2012: Cost-effectiveness of Adult Vaccination Strategies Using Pneumococcal Conjugate Vaccine Compared with Pneumococcal Polysaccharide Vaccine. (Economic evaluation) [16]

Population	Adults 50 years of age or older
Intervention	PCV13
Comparator	PPSV23
Outcome	Pneumococcal disease cases prevented, cost-effectiveness
Setting	USA

This study presents an update of Smith et al. 2008 which examines the cost-effectiveness of PCV13 compared to PPSV23. The VE estimates for PPSV23 are taken from this previous study and the effectiveness of PCV13 against IPD and NPP is also estimated via a Delphi expert panel. These new estimates are given for 50-year old, healthy persons, 65-year old healthy persons and immunocompromised persons of all ages. Reduced effectiveness (waning) is given at 1, 3, 5, 10 and 15 years after vaccination.

Vila-Corcoles et al. 2006: Protective Effects of the 23-Valent Pneumococcal Polysaccharide Vaccine in the Elderly Population: The EVAN-65 Study. (Cohort) [17]

Population	Adults 65 years of age or older
Intervention	PPSV23
Comparator	*NA*
Outcome	invasive pneumococcal disease, pneumococcal pneumonia, overall pneumonia rate, death due to pneumonia

Setting	8 primary health care centers in Tarragona, Spain, January 2002 through April 2005

This study examined the VE of PPSV23 in community-dwelling persons ≥65 years of age against IPD, pneumococcal pneumonia, overall pneumonia and pneumonia-related mortality. The prospective cohort study collected data on 11,241 subjects and lasted from January 2002 until April 2005. 4,986 persons were already vaccinated at the begin of the study of which 4,314 had been vaccinated within 2 years before the study. 1,449 of the 6,255 unvaccinated persons at the begin were vaccinated during the study period. The multi-variable Cox model showed a protective effect of PPSV23 against serotype-related IPD of HR 0.61 [95%CI 0.13-2.76], a HR of 0.60 [95%CI 0.22-1.65] against all-type IPD, a HR of 0.45 [95%CI 0.15-1.40] against bacteremic pneumococcal pneumonia and a HR of 0.61; [95%CI 0.35–1.06] against overall pneumococcal pneumonia.

Vila-Corcoles et al. 2009: Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: A matched case–control study. (Case control) [18]

Population	Adults 50 years of age or older
Intervention	PPSV23
Comparator	No vaccination
Outcome	Pneumococcal pneumonia (bacteremic and non-bacteremic), stratified by vaccine- and non-vaccine serotypes
Setting	19 participating PHCCs and Laboratory Departments of 3 reference hospitals in Tarragona, Spain, January 2002 to April 2007.

In this study the VE of PPSV23 is estimated via a matched case control study of 304 cases of radiographically confirmed pneumococcal pneumonia above the age of 50 years and 608 matched controls taken from January 2002 to April 2007. Study participants are considered vaccinated if they received the vaccine at least 14 days before the onset of the disease. No information is given on the average duration of vaccine protection. VE is calculated via a conditional logistic regression resulting in adjusted odds ratios (OR). Against all pneumococcal pneumonia the VE was 48% [OR: 0.52; 95%CI 0.37–0.73] and more effective against bacteremic pneumococcal pneumonia with 66% [OR: 0.34; 95%CI 0.27–0.66]. VE against vaccine-type serotypes was 76% [OR: 0.24; 95%CI 0.09–0.66].

PPSV9

Klugmann et al. 2003: A Trial of a 9-Valent Pneumococcal Conjugate Vaccine in Children with and Those without HIV Infection. (RCT) [19]

Population	Infants
Intervention	PPSV9 + Haemophilus influenzae type b conjugate vaccine administered at 6, 10, and 14 weeks of age
Comparator	Placebo + Haemophilus influenzae type b conjugate vaccine administered at 6, 10, and 14 weeks of age
Outcome	Invasive pneumococcal disease
Setting	Soweto, South Africa

The efficacy of a PPSV9 vaccine was evaluated on 19,922 children with and without HIV vaccinated at 6, 10 and 14 weeks of age in Lesotho, South Africa, and compared to 19,914 controls. It is unclear what the distribution of the HIV serostatus of the children is, but results are reported stratified by HIV status. In HIV-negative children, the VE against IPD against the serotypes covered by PPSV9 was 83% [95%CI 39%-97%] with 3 cases in the vaccinated group and 17 in the control group. Efficacy

against pneumonia is not reported stratified by serotype and is estimated to be 20% [95%CI 2%-35%] in HIV-negative children.

PPSV

Moberley et al. 2008: Vaccines for preventing pneumococcal infection in adults. (Meta-analysis) [20]

Population	Adults ≥16 years
Intervention	PPSV vaccination
Comparator	No vaccination, placebo, control vaccines
Outcome	Invasive pneumococcal disease All-cause pneumonia mortality
Setting	worldwide

This study presents the results of a Cochrane systematic review and meta-analysis on the VE of PPSV vaccines in persons ≥16 years of age. 22 studies are included in the meta-analysis. Unfortunately, the studies are not group by valency and the results are pooled of 7 studies using 23-valent vaccine, 1 study on a 17-valent, 8 studies on a 14-valent, 2 studies on 12-valent, 3 studies on 6-valent, 1 study on 2-valent and 1 study with an unspecified vaccine. The meta-analysis found a strong VE against IPD of 74% (95% CI 55% to 86%) [OR 0.26; 95%CI 0.15-0.46], but inconclusive evidence against all cause pneumonia with a VE of 29% [OR 0.71; 95%CI 0.52-0.97]. Immunosuppressed persons seem to be less protected. No estimates for vaccine-serotypes are reported. No stratification by age or time since vaccination is performed.

Moberley et al. 2013: Vaccines for preventing pneumococcal infection in adults. (Meta-analysis) [21]

Population	Adults ≥16 years
Intervention	PPSV vaccination
Comparator	No vaccination, placebo, control vaccines
Outcome	Invasive pneumococcal disease All-cause pneumonia mortality
Setting	worldwide

This paper is an update on the previously published Cochrane meta-analysis of Moberley et al. 2008. The analysis includes three more studies, all of which examine the effectiveness of PPSV23. The results against IPD are fairly similar with a VE of 74% [OR 0.26, 95%CI 0.14-0.45] and higher than in the previous analysis with 46% [OR 0.54, 95%CI 0.43-0.67] against all-cause pneumonia.

References

1. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J. 2000;19:187–95.
2. Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–25. doi:10.1056/NEJMoa1408544.

3. Frenck RW, Fiquet A, Gurtman A, van Cleeff M, Davis M, Rubino J, et al. Immunogenicity and safety of a second administration of 13-valent pneumococcal conjugate vaccine 5 years after initial vaccination in adults 50 years and older. Vaccine. 2016;34:3454–62. doi:10.1016/j.vaccine.2016.04.093.
4. Patterson S, Webber C, Patton M, Drews W, Huijts SM, Bolkenbaas M, et al. A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults). Trials in Vaccinology. 2016;5:92–6. doi:10.1016/j.trivac.2016.04.004.
5. van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJM. The Impact of Age on the Efficacy of 13-valent Pneumococcal Conjugate Vaccine in Elderly. Clin Infect Dis. 2015;61:1835–8. doi:10.1093/cid/civ686.
6. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30:6802–8. doi:10.1016/j.vaccine.2012.09.019.
7. Diao W-Q, Shen N, Yu P-X, Liu B-B, He B. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. Vaccine. 2016;34:1496–503. doi:10.1016/j.vaccine.2016.02.023.
8. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS ONE. 2017;12:e0169368. doi:10.1371/journal.pone.0169368.
9. Gutiérrez Rodríguez MA, Ordobás Gavín MA, García-Comas L, Sanz Moreno JC, Córdoba Deorador E, Lasheras Carbajo MD, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008–2011. Eurosurveillance 2014. doi:10.2807/1560-7917.ES2014.19.40.20922.
10. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009;180:48–58. doi:10.1503/cmaj.080734.
11. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. Vaccine. 2016;34:1540–50. doi:10.1016/j.vaccine.2016.02.024.
12. Middleton DB, Lin CJ, Smith KJ, Zimmerman RK, Nowalk MP, Roberts MS, Fox DE. Economic evaluation of standing order programs for pneumococcal vaccination of hospitalized elderly patients. Infect Control Hosp Epidemiol. 2008;29:385–94. doi:10.1086/587155.
13. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, Gomez-Bertomeu F, Figuerola-Massana E, Raga-Luria X, Hospital-Guardiola I. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged ≥ 60 years: 3 years of follow-up in the CAPAMIS study. Clin Infect Dis. 2014;58:909–17. doi:10.1093/cid/ciu002.
14. Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325:1453–60. doi:10.1056/NEJM199111213252101.
15. Smith KJ, Zimmerman RK, Lin CJ, Nowalk MP, Ko F-S, McEllistrem MC, Roberts MS. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine. 2008;26:1420–31. doi:10.1016/j.vaccine.2008.01.007.

16. Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012;307:804–12. doi:10.1001/jama.2012.169.
17. Vila-Córcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodríguez T, Llor C. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis. 2006;43:860–8. doi:10.1086/507340.
18. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, Ochoa-Gondar O, Diego C de, Valdivieso A, et al. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. Vaccine. 2009;27:1504–10. doi:10.1016/j.vaccine.2009.01.013.
19. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349:1341–8. doi:10.1056/NEJMoa035060.
20. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008:CD000422. doi:10.1002/14651858.CD000422.pub2.
21. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013:CD000422. doi:10.1002/14651858.CD000422.pub3.

S4 Table 1: Base-case incidence rates per 100,000 people and vaccine effectiveness parameters in the studies included into the quality assessment of economic evaluation (n=13).

Authors, year, country	Age groups (y.o.)	Rates per 100,000 population used in base-case analysis						Source of incidence
		IPD indication			non-IPD		of pneumococcal origin	
Jiang et al, 2012, Germany [1]	16–44 45-64 65-74 ≥75	IPD 2.5 8.8 24.1 10.3	PM is 8.2% of IPD	PMS is 52% of PM	NBP 33.0-3581 different age groups as for IPD		NBPP = 40% of NBP; No vaccine type division	IPD incidence is also given for vaccine-related serotype groups. Estimated based on findings from the German prospective laboratory-based surveillance [2]. NBP: nationwide mandatory performance measurement programme in healthcare quality[3].
Mangen et al, 2015, Netherlands [4]	18-49 50-64 65-74 75-84 >84	IPD LR 3.1 7.0 11.5 16.4 48.3	IPD MR 39.9 53.0 65.4 81.8 107	IPD HR 183.1 269.0 244.0 148.8 101.8	Inpatient NBP 71-2450	Outpatient NBP 2011-5044	10% of NBP are attributable to PCV13 vaccine serotypes	Incidence of IPD, inpatient- and outpatient CAP is stratified by age- (18-≥84y.o) and risk-group. Serotype (PCV13 and nonPCV13) distribution of IPD stratified by age-group. IPD: Dutch surveillance from nine Dutch sentinel microbiology laboratories[5]. in-CAP: CAP-START and DHC: cluster-randomized-cross-over trial in seven Dutch hospitals. out-CAP: Julius GP Network - database containing anonymous routine healthcare data from the digital patient records of 45 GP practices
Blommaert et al, 2016, Belgium [6]	45-64 65-74 ≥75	PM 0.9 1.3 1.0	PB 17.4 40.9 95.7	PS 1.9 5.0 10.3	NBP 361 650 1053		27.3% of NBP	IPD or non-IPD cases per year are calculated using the disease-specific hospitalization rates. Incidence for BP and NBPP are calculated based on assumptions which are tested in SA: age-independent proportion BP and case-fatality are equal for BP and NBP. Source: the Belgian government's hospitalisations database
R-G-Moro et al, 2016, Spain [7]	50-64 65-74 75-84 85-99	IPD 91.0 91.0 91.0 91.0			In-NBP 201.8 594.9 1535.1 3491	Out-NBP 143.2 422.0 1089 2476.5	Not given	IPD: [8]; nIPD: a retrospective epidemiological study, Spain[9]; data from the Centers for Disease Control and Prevention; No proportion of all cause-NBP cases attributable to vaccine serotypes is given.
Stoecker et al, 2016. USA [10]	50-64 ≥65	IPD healthy 8.62 15.06		IPD HR 33.71 47.63	in-NBPP healthy 285.2 HR: 600	out-NBPP healthy 1375.2 HR: 1375.2	10% NBPP due to PCV13 serotypes	IPD: Active Bacterial Core Surveillance data of 2013, unpublished data in- NBPP: analysis of data from a private inpatient discharge record database by Simonsen et al. (2014) [11] out-NBPP: population-based pneumonia surveillance, Nelson et al. (2008)[12]
van Hoek et al, 2016, England [8]	65-74 75-84 ≥85	IPD 1.1 2.04 3.76			NBP by PCV13 serotypes 4.17 6.55 21.45		Vaccine-type incidence of IPD is reported for modelled years.	Vaccine-type incidence of IPD is reported for modelled years. Here are the IPD rates caused by PCV13 serotype for 2015/2016y. In 2018/2019 a steady-state is assumed Source: surveillance data collected by Public Health England: July-June from 2002/03 to 2013/2014 [13].
Dirmesropian et al, 2017, Australia [14]	65-69 70-74 75-79 80-84	PM 0.98 1.17 1.65 0.93	PB 0.98 1.17 1.65 0.93	PP 5.73 7.53 10.08 12.78	NBP 536 853 1269 2073		IPD by PCV13 types: 0.284, 0.293, 0.299, 0.324 0.330 nIPD by PCV13: 0.139 of NBP IPD by PPSV23 types: 0.678, 0.597,0.546,0.521, 0.518 for age	Vaccine-type incidence of IPD is reported for modelled years. Here are the IPD rates caused by PCV13 serotype for 2015/2016y. In 2018/2019 a steady-state is assumed

	≥85	0	0	18.15	3502			groups	Source: surveillance data collected by Public Health England: July-June from 2002/03 to 2013/2014 [13].
Heo et al, 2017, Korea [15]		IPD			NBPP			IPD by: PPSV23 types: 59.5%; PCV13 types: 35.1%; PPSV23+PCV13 types: 60.8% nIPD by: PPSV23 types: 49.8% PCV13 types 35.2% PPSV23+PCV13 types 53.4%	Age-specific incidence rates for IPD and NPP are based on data from a national catchment area. Risk-group specific incidence rates are calculated based on the assumption that the risk ratio of CAP versus the general population is transferable to IPD and NPP.
		LR	MR	HR	LR	MR	HR		
	19-49	0.9	2.2	4.1	4.9	12.3	23.3		
	50-64	4.3	10.9	20.5	30.5	76.8	145.7		
	65-74	17.6	19.4	44.1	214	238	540		
	≥75	64.3	52.8	100.9	710	578	1113		
Chen et al, 2018, Australia [16, 17]		PM	BPP		in-NBP	out-NBP		nIPD**:** 13.9% of NBP	Australian Department of Health and Ageing. National Notifiable Disease Surveillance System (NNDSS), Publics datasets
	50-64	0.61	1.95		519	1624.1			
	65-69	1.20	4.79		519	1624.1			
	70-74	1.31	3.78		815	1624.1			
	75-79	1.68	5.20		1224	3333.3			
	80-84	0.92	4.81		2062	3333.3			
	≥85	0.00	7.61		3373	3333.3			
Thorrington et al, 2018, Netherlands [18]	≥60	IPD due to PPSV23-PCV13 types in 2015: 20.63 IPD due to non-vaccine types in 2015: 6.75 the pre-vaccination steady state of IPD 54/100,000							Incidence is stratified by age and the probability of IPD and CAP were age-specific and data obtained from the Dutch (registry) data. Values are calculated from the equations given in appendix 1.
Willem et al, 2018, Belgium[19]		PM	IP	total IPD	NBP	non-IPP		IPD by: PPSV23 types - 66% of all IPD PCV13 types - 25% of all IPD nIPD by: PCV13 -25% of non-IPP PPSV23 -51% of non-IPP hospitalised nIPP:82.7%	IPD data is from the National Reference Centre (NRC), 2015; all-cause &PP: INTEGO 2013 R81 codes and pooled estimates from Capelastegui et al (2012)[20] and Holm et al (2007) [21].
	50-64	1.3	12.4	14.9	598.8	57			
	65-74	1.1	22.1	25.5	672.2	64			
	75-84	1.6	32	36.8	1009	69.1			
	≥85	3.6	69.6	80.2	1504.7	143.3			
Kuchenbecker et al, 2018, Germany[22]		PM	PB		In-NBP	Out-NBP		IPD by PCV13 types - 29.3% PPSV23 types - 58.7-74.5% nIPD PCV13 types - 29.3% PPSV23 types – 29.9% of NBP	Incidence is given for age- and health risk group. Here age groups 18-49y.o and 50-59y.o are omitted. IPD incidence rates are derived based on the data of a publication on IPD in North-Rhine Westphalia Germany by Reinert et al. (2005)[2] extrapolating the incidence of the overall population; health-risk adjustment is based on van Hoek et al. (2012)[23]. The study refers to four sources which are used to derive incidence rates without reporting the methods.
	LR:								
	60-64	0.02	0.33		84.03	119.04			
	65-74	0.18	6.87		243.77	345.35			
	75-99	0.08	3.09		1059.8	1501.4			
	MR:								
	60-64	0.14	2.07		323.57	458.4			
	65-74	0.40	14.9		938.7	1329.8			
	75-99	0.18	6.73		4021	5781.6			
	HR:								
	60-64	0.38	5.67		193.66	274.35			
	65-74	2.14	80.4		561.8	795.9			
	75-99	0.96	36.1		2442.5	3460.3			

Abbreviations: all-CAP – all-cause community-acquired pneumococcal pneumonia; BPP - bacteraemic pneumococcal pneumonia; IP – invasive pneumonia; NBBP – non-bacteraemic pneumococcal pneumonia; NBP – non-bacteremic pneumonia; NPP - non-bacteremic pneumococcal pneumonia; NVT – non-vaccine type serotypes; PCV13-PCV7 - serotypes in PCV13, but not in PCV7;PB – pneumococcal bacteraemia, PM – pneumococcal meningitis; PP – Pneumococcal pneumonia; PPSV23-PCV13 - serotypes in PPSV23, but not in PCV13; PS - pneumococcal septicaemia

References

1. Jiang Y, Gauthier A, Annemans L, van der Linden M, Nicolas-Spony L, Bresse X. Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. Expert Rev Pharmacoecon Outcomes Res. 2012;12:645–60. doi:10.1586/erp.12.54.
2. Reinert RR, Haupts S, van der Linden M, Heeg C, Cil MY, Al-Lahham A, Fedson DS. Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001-2003. Clin Microbiol Infect. 2005;11:985–91. doi:10.1111/j.1469-0691.2005.01282.x.
3. Ewig S, Birkner N, Strauss R, Schaefer E, Pauletzki J, Bischoff H, et al. New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. Thorax. 2009;64:1062–9. doi:10.1136/thx.2008.109785.
4. Mangen M-JJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46:1407–16. doi:10.1183/13993003.00325-2015.
5. van Deursen AMM, van Mens SP, Sanders EAM, Vlaminckx BJM, Melker HE de, Schouls LM, et al. Invasive pneumococcal disease and 7-valent pneumococcal conjugate vaccine, the Netherlands. Emerging Infect Dis. 2012;18:1729–37. doi:10.3201/eid1811.120329.
6. Blommaert A, Bilcke J, Willem L, Verhaegen J, Goossens H, Beutels P. The cost-effectiveness of pneumococcal vaccination in healthy adults over 50: An exploration of influential factors for Belgium. Vaccine. 2016;34:2106–12. doi:10.1016/j.vaccine.2016.03.003.
7. Rodriguez Gonzalez-Moro JM, Menendez R, Campins M, Lwoff N, Oyaguez I, Echave M, et al. Cost Effectiveness of the 13-Valent Pneumococcal Conjugate Vaccination Program in Chronic Obstructive Pulmonary Disease Patients Aged 50+ Years in Spain. Clin Drug Investig. 2016;36:41–53. doi:10.1007/s40261-015-0345-z.
8. van Hoek AJ, Miller E. Cost-Effectiveness of Vaccinating Immunocompetent /=65 Year Olds with the 13-Valent Pneumococcal Conjugate Vaccine in England. PLoS ONE. 2016;11:e0149540. doi:10.1371/journal.pone.0149540.
9. Sicras-Mainar A, Ibáñez-Nolla J, Cifuentes I, Guijarro P, Navarro-Artieda R, Aguilar L. Retrospective epidemiological study for the characterization of community-acquired pneumonia and pneumococcal pneumonia in adults in a well-defined area of Badalona (Barcelona, Spain). BMC Infect Dis. 2012;12:283. doi:10.1186/1471-2334-12-283.
10. Stoecker C, Kim L, Gierke R, Pilishvili T. Incremental Cost-Effectiveness of 13-valent Pneumococcal Conjugate Vaccine for Adults Age 50 Years and Older in the United States. J Gen Intern Med. 2016;31:901–8. doi:10.1007/s11606-016-3651-0.
11. Simonsen L, Taylor RJ, Schuck-Paim C, Lustig R, Haber M, Klugman KP. Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: a time series analysis. Lancet Respir Med. 2014;2:387–94. doi:10.1016/S2213-2600(14)70032-3.
12. Nelson JC, Jackson M, Yu O, Whitney CG, Bounds L, Bittner R, et al. Impact of the introduction of pneumococcal conjugate vaccine on rates of community acquired pneumonia in children and adults. Vaccine. 2008;26:4947–54. doi:10.1016/j.vaccine.2008.07.016.
13. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MPE, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: An observational cohort study. The Lancet Infectious Diseases. 2015;15:535–43. doi:10.1016/S1473-3099(15)70044-7.

14. Dirmesropian S, Wood JG, MacIntyre CR, Beutels P, McIntyre P, Menzies R, et al. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) in older Australians. Vaccine. 2017;35:4307–14. doi:10.1016/j.vaccine.2017.06.085.
15. Heo JY, Seo YB, Choi WS, Lee J, Noh JY, Jeong HW, et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLoS ONE. 2017;12:e0177342. doi:10.1371/journal.pone.0177342.
16. Chen C, Wood JG, Beutels P, Menzies R, MacIntyre CR, Dirmesropian S, et al. The role of timeliness in the cost-effectiveness of older adult vaccination: A case study of pneumococcal conjugate vaccine in Australia. Vaccine. 2018;36:1265–71. doi:10.1016/j.vaccine.2018.01.052.
17. Chen C, Beutels P, Newall AT. Evolution over time in the cost-effectiveness of pneumococcal conjugate vaccine (PCV13) in older Australians due to herd protection from infant vaccination. Vaccine. 2018;36:2057–60. doi:10.1016/j.vaccine.2018.03.006.
18. Thorrington D, van Rossum L, Knol M, Melker H de, Rümke H, Hak E, van Hoek AJ. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS ONE. 2018;13:e0192640. doi:10.1371/journal.pone.0192640.
19. Willem L, Blommaert A, Hanquet G, Thiry N, Bilcke J, Theeten H, et al. Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. Hum Vaccin Immunother. 2018:1–12. doi:10.1080/21645515.2018.1428507.
20. Capelastegui A, España PP, Bilbao A, Gamazo J, Medel F, Salgado J, et al. Etiology of community-acquired pneumonia in a population-based study: Link between etiology and patients characteristics, process-of-care, clinical evolution and outcomes. BMC Infect Dis. 2012;12:134. doi:10.1186/1471-2334-12-134.
21. Holm A, Nexoe J, Bistrup LA, Pedersen SS, Obel N, Nielsen LP, Pedersen C. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract. 2007;57:547–54.
22. Kuchenbecker U, Chase D, Reichert A, Schiffner-Rohe J, Atwood M. Estimating the cost-effectiveness of a sequential pneumococcal vaccination program for adults in Germany. PLoS ONE. 2018;13:e0197905. doi:10.1371/journal.pone.0197905.
23. van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, Miller E. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65:17–24. doi:10.1016/j.jinf.2012.02.017.

S5 Results of quality assessment with EVIDEM of the selected studies (n=13)

Table S5.1: Brief results of assessment of quality of economic evaluations with EVIDEM (n=13).

Authors, year, country	Results of quality assessment of economic evaluation with EVIDEM (for detail see supplement, S5:EVIDEM)
Jiang et al, 2012, Germany [1]	*Completeness and consistency*: The reporting lacks description of the modelling approach to the waning of VE against NBPP and for immunocompromised people. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: Validity and relevance of the study are limited due to application of foreign data (stemming from clinical and cost-effectiveness studies) to inform the model induced by lack of the corresponding German data. These include QALY weights, indirect effects, mortality by serotype. Single-cohort model does not provide accurate estimates of incidence when equilibrium is not reached. Score:1☐ 2☒ 3☐ 4 ☐
Mangen et al, 2015, Netherlands [2]	*Completeness and consistency*: The paper has some gaps about applied age-specific VE and applied resources used per case. Score: 1☐ 2☐ 3☐ 4 ☒ *Relevance and validity*: The study assumes that herd effects of PCV7 childhood vaccination have reached full presence at the time of the initiation and infant vaccination with PCV10 has no indirect effects of for adults. Score:1☐ 2☐ 3☒ 4 ☐
Blommaert et al, 2016, Belgium [3]	*Completeness and consistency*: The paper has some gaps in reporting the exponential waning of VE applied in SA. Score: 1☐ 2☐ 3☐ 4 ☒ *Relevance and validity*: Chosen population, comparator, perspective, time horizon, discount rates, costs and health outcomes are relevant. Applied epidemiological - and cost data are obtained from the national sources The study examines the effects of the uncertainty around the duration of the vaccine protection and indirect effects of the paediatric vaccination as well as around the incidence of non-bacteremic hospitalized pneumonia on the cost-effectiveness estimates. Score:1☐ 2☐ 3☐ 4 ☒
Rodriguez Gonzalez-Moro et al, 2016, Spain [4]	*Completeness and consistency*: Modelling of herd effects and calculation of applied costs are not transparently described. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: The evaluated vaccination strategy is limited to vaccinating individuals with COPD. Applied costs are limited to the direct costs per case of the disease due to the taken perspective. The costs are aggregated. The target population is difficult to compare to the population of the studies in which VE data is obtained. The study models a cohort of COPD patients and assumes that the patients are immunocompetent. IPD incidence is obtained from a study conducted in England looking at clinical conditions which cause a risk for IPD development. Modelling of the herd effects of the paediatric vaccination with PCV13 are not described making it difficult to assess its plausibility. Score:1☐ 2☒ 3☐ 4 ☐
Stoecker et al, 2016. USA [5]	*Completeness and consistency*: The paper has minor gaps in reporting the waning rate of VE and estimation of costs per case, namely applied resources used per case. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: IPD is not divided by specific diseases in the cost calculations and reporting the results. The reported costs are aggregated as cost per case for each considered disease making it difficult to conclude whether all relevant costs are included.

	Score:1☐ 2☐ 3☒ 4 ☐
van Hoek et al, 2016, England [6]	*Completeness and consistency*: The reporting can be considered partly transparent. The paper has gaps about the structure of the developed model, applied PPSV23 VE, estimation of costs per case and details of the sensitivity analyses. The aggregated costs per case are given. Score: 1☐ 2☒ 3☐ 4 ☐ *Relevance and validity*: The study does not contain a description of the model design and methods of sensitivity analyses making it hard to evaluate validity and relevance. Epidemiological parameters, costs and utilities are based on the national data. The study applies a conservative approach to the duration of the vaccine protection. Score: 1☐ 2☐ 3☒ 4 ☐
Dirmesropian et al, 2017, Australia [7]	*Completeness and consistency*: The model is very detailed as many parameters are age-stratified and almost all parameter values are reported. However, some information is not stated (e.g., vaccination rates) or it is ambiguous which values are used in the base case (e.g. PCV13 vaccine efficacy). Some information on the resource use is either missing or the costing is simplified. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: Epidemiological- and cost data is obtained from the national sources. The utilities are taken from study conducted in Netherlands. Regarding the event pathway it is not clear how mutually exclusive the different health states are, e.g. if a patient that is hospitalized for CAP can also have GP visits and if there is a treatment pathway used for the costing. Score: 1☐ 2☐ 3☒ 4 ☐
Heo et al, 2017, Korea [8]	*Completeness and consistency*: The study reports all of the main input parameter values in great detail but is less precise on the perspective and the time horizon of the model. Model structure contains “disabled” disease state but neither costs and nor QALY losses are given for it. The reference year for the costs is not clearly stated. No figures or sources of background mortality are given. Results are reported not in detail. All scenarios are only compared to a “no vaccination” scenario and no ICER is reported comparing the different strategies. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: The validity of the study is difficult to assess due to incompleteness in reporting cost calculations, model structure, discounting and the results. The time horizon is not long enough to capture all meaningful differences in costs and outcomes. It is set to 15 years in the base case and no sensitivity analyses are performed. As the age group being vaccinated spans 20 years and vaccine efficacy is longer than 15 years, a longer time horizon may lead to different results. The authors only state to conduct the analysis in a “societal context”, which can be interpreted as a societal perspective. No guidelines are cited, making it difficult to judge the validity of the perspective in the Korean context. Indirect cost calculations seem to be missing for some disease states or manifestations of IPD. Indirect costs seem only to be calculated for the productivity loss of the patient for the length of stay. It is unclear whether forgone productivity loss due to pre-mature mortality is included or if the Human Capital or the Friction Cost approach have been used. Discount rate is assumed without reporting a reference and no sensitivity analysis on it is conducted. Values in the deterministic sensitivity analysis are considered to be unusual and the corresponding tornado plot looks skewed. Not all critical values are covered in SA. Score: 1☐ 2☒ 3☐ 4 ☐
Chen et al, 2018, Australia [9]	*Completeness and consistency*: The study reports most parts of the study in great detail, but this study paper represents an adaption of a previous paper and is used to analyse effects of the age at vaccination on the cost-effectiveness. The study lacks a graphical representation of the model. Nearly all parameters of the model are given, although the costing for the different health states seems to have a very simple treatment pathway. CAP fatality rates are not reported. No sensitivity analyses are conducted which is justified by the focus of the study. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: The study question is not a classical cost-effectiveness analysis, but on the timeliness of PCV13 vaccination, i.e. what the optimal age for the vaccination. The target population, comparator, perspective, time horizon, discounting and costs are relevant. QALY losses are taken from a Dutch study and combined with the Australian population norms. Score: 1☐ 2☐ 3☒ 4 ☐
Chen et al, 2018, Australia [10]	*Completeness and consistency*: The paper reports the results of an additional analysis conducted with the model from a previously published study[9]. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: The study performs a cost-effectiveness analysis of vaccination of elderly with PCV13, comparing two different scenarios of the future serotype evolution, probably against a “no vaccination” scenario. The study design is of the previous study by Chen et al (2018) [9]. The study can be seen as a sensitivity analysis to that study, looking at the impact of the assumptions about the serotype evolution after the introduction of a new vaccination on the cost-effectiveness estimate. The question is relevant and the design appropriate to answer this question.

	Score: 1☐ 2☐ 3☐ 4 ☒
Thorrington et al, 2018, Netherlands [11]	*Completeness and consistency*: This study reports some parts of the economic evaluation in great detail, especially parts about incidence and mortality data, costing and QALY parts are rather simplified. The values for those cost and QALY parameters are taken from another modelling study. Only indirect costs are considered and split into IPD and CAP. No reference year of the costs is stated. The model is described as a static model and no illustration of the model is given. There is no information about the cycle length, but a yearly time step can be assumed. Disease states are not clearly identified, although IPD and CAP can be assumed to be the modelled health states. No probabilistic sensitivity analysis is performed. No ranges for the deterministic sensitivity analyses are given. Only the different mortality-parameters are age-specific. Sources of population sizes, background mortality/life-expectancy are not clearly stated. Score: 1☐ 2☐ 3☒ 4 ☐ *Relevance and validity*: The study is relevant, but in many cases, there are unnecessary simplifications in the model, i.e. ignoring age-specific data, no prices-resources framework and arbitrary scenario/sensitivity analyses. The population is hardly comparable with the trial population and age-specific results from the trial are not incorporated. The event pathway includes only IPD, CAP and death are included in the model without further stratification. IPD mortality is age- and vaccine-type specific from the Dutch surveillance data. CAP mortality is taken from a German source. No age-specific costs are used. Administration costs are omitted. QALY losses are estimated to be identical for IPD and CAP and another model is referenced as the source. No other information is provided about the values of population norms, the duration of the health states or the utility decrements. Score: 1☐ 2☐ 3☒ 4 ☐
Willem et al, 2018, Belgium [12]	*Completeness and consistency*: Minor limitation is that the ranges for PSA cannot be found for all parameters and values of the distributions for PSA are only reported for the incidence of pneumonia and the case fatality ratio. Score: 1☐ 2☐ 3☐ 4 ☒ *Relevance and validity*: The study design is relevant. Event pathway includes all relevant disease stages. For meningitis, long-term effects of hearing loss and neurological sequalae are considered and death may occur from any state. The events are mutually exclusive. Vaccine failure is considered in the model structure. Most of the data stem from the national sources. Sensitivity analyses are conducted on a wide range of parameters. The target population is relevant and represents the intended target group of the intervention. But it does not coincide with the study population in CAPITA and with the PPSV23 VE study population by Andrews et al. (2012) [13]. Score: 1☐ 2☐ 3☐ 4 ☒
Kuchenbecker et al, 2018, Germany [14]	*Completeness and consistency*: The study adopts an earlier developed US microsimulation framework with Markov-type process by Weycker et al (2012) [15]. The model structure is incomplete reported. The study shows inconsistency in the reporting the methods applied to estimation of the waning rate and calculation of the herd effects of PCV7/PCV13. Table 2 shows inconsistency in the reporting of the values of VE for PCV13 ag IPD in the low risk group of 65-74 y.o., for year 10 (VE =1%) and for PPSV23 ag IPD for high risk group of 50-59y.o. for year 10 (VE =37%, though initial VE =15%). Approach to the waning of protection is inconsistently described: main text reports exponential function, the supplemental material stats a liner interpolation. The costs per unit are not reported. The representation of the applied parameters for PSA is not intuitively interpretable. No reference year for the costs is reported. Score: 1☐ 2☒ 3☐ 4 ☐ *Relevance and validity*: Due to incompleteness in reporting it is difficult to assess plausibility and relevance in the important dimensions of the study. The event pathway applied in the model is not described in detail. The study refers to four sources which are used to derive incidence rates without reporting the methods of how the data is adjusted making it difficult to assess the relevance. IPD age trends differ from those of NBPP (inpatient and outpatient) incidence showing for people over 60y.o. largest rates in 65-74y.o age group. NBPP (inpatient and outpatient) incidence shows lower rates for high health risk groups than for moderate-risk groups for all age groups. The study lacks a description of the methods for calculation of the presented cumulative herd effects from the reported predicted serotype-distributions in IPD by that making it difficult to assess relevance of applied herd effects. It is not clear how the applied values of the herd effects for nIPD are obtained. Applied PPSV23 VE is based on the estimates by a Delphi expert panel [16]. The authors do not justify applied linear interpolation of VE over age-year increments. Uncertainty of the assumption that PCV13 VE is 50% of the values of PPSV23 VE applied in extrapolations to calculate age-specific PCV13 VE values and waning rates is not tested. Reporting of the ranges applied in the PSA is not complete and the table is not easy to interpret. Score: 1☐ 2☒ 3☐ 4 ☐

Abbreviations: CAP – community-acquired pneumococcal pneumonia; CE – cost-effectiveness; CI – confidence interval; ICER – incremental cost-effectiveness ratio; IPD – invasive pneumococcal diseases; LYG – life years gained; NBPP – non bacteraemic pneumococcal pneumonia; PSA – probabilistic sensitivity analysis; QALY – quality adjusted life year; SA – sensitivity analyses; VE – vaccine effectiveness; WTP – willingness-to-pay

Table S5.2: Full results of assessment of quality of economic evaluations with EVIDEM (n=13).

An economic evaluation was considered to be relevant and valid when it presented relevancy of the chosen population, comparator, perspective, time horizon, discount rates, costs and health outcomes; applied epidemiological – and cost data were obtained from the national sources; sensitivity analyses covered the most critical parameters within a valid range; the methods applied in modelling waning of the vaccine protection were clearly described; and the applied indirect effects of the childhood vaccination were based on epidemiological data.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23) **Setting:** Germany			**Study:** Jiang, Yiling; Gauthier, Aline; Annemans, Lieven; van der Linden, Mark; Nicolas-Spony, Laurence; Bresse, Xavier (2012): Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. In Expert review of pharmacoeconomics & outcomes research 12 (5), pp. 645–660. DOI: 10.1586/erp.12.54.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	This study reports all the dimensions of the economic evaluation. The reporting can be considered complete and transparent. The information is consistent across the sections of the study.	**1** ☐ **Many gaps/ inconsistent** **2** ☐ **3** ☒ **4** ☐ **Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The study defines the target population as German adults (aged 18 years and older) eligible for PPSV23 vaccination and who would receive the vaccination in 2011.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: vaccination of elderly and at-risk adults in Germany with PPSV23 against IPD and NBPP. Based on the German recommendation at the time of the study it was assumed that only people younger than 60 years at initial vaccination would receive revaccination after 5 years of the initial vaccination.	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The study includes a population-based Markov model with cycle length of 1 year. The structure is presented by a figure without attribution of the cost and transition probabilities between the events. The flow of events is described in the main text. The model incorporates possible impact of vaccinating children with PCV7 and PCV13 by including future changes into the epidemiology of IPD in adults. Indirect protection of vaccination adults with PPSV23 is not included due lack of evidence.	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The hypothetical vaccination program is compared with no vaccination.	

5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis was performed from the third-party payer's perspective and societal perspective
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	Cost-effectiveness analysis of adult vaccination with PPSV23 compared to no vaccination. Health outcomes are measured in quality-adjusted life years (QALYs). The study assumes an arbitrary threshold of €50,000 per QALY gained as the primary threshold of cost–effectiveness because "the German health technology assessment authorities do not set a fixed threshold of incremental cost–effectiveness ratio (ICER) and the threshold of €50,000/ QALY is commonly used in this context. A secondary threshold of ICER is assumed of €30,000/ QALY.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* IPD and nonbacteremic pneumonia incidence across age groups are presented for 2005 and the sources are described. The IPD incidence is given for vaccine-related serotype groups. The methods applied to predict the impact of the childhood vaccination on the incidence are described and the applied parameters are provided. The risk parameters (risk of IPD, risk of death, case-fatality ratios) are given. *Vaccine effectiveness:* VE parameter is not age-specific due to the source used to obtain the data. Against IPD: 74% for immunocompetent- and 35% for immunocompromised individuals [17] Against NBPP: 39% for immunocompetent- and 0% for immunocompromised individuals [18] Duration of protection: parameters are given as proportions of remaining VE in percent for each year over 10 years where the individuals no longer protected after 8 years from the initial vaccination. References are given however rationale is not provided. We calculated years of full protection and average duration of protection with PPSV23 against IPD: 5.3 years of full protection and 2.7 years of average duration of protection against IPD for immunocompetent people. It is not clear whether the same waning function is applied for the VE against NBPP and for immunocompromised people. Coverage is 3% of eligible people. Proportion of the vaccinated receiving revaccination is 3% of vaccinated people.
8	Time horizon	Is the time horizon reported?	The time horizon is defined as until death or 100 years of age.
9	Discount rate	Is the discount rate reported?	Discount rate is 3% for cost and QALY. In SA: 0%, 5%
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Univariate- and probabilistic sensitivity analyses are conducted for a wide range of parameters. The ranges are reported with the respective references.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	ICER of PPSV23 vaccination vs no vaccination: €17,065/ QALY gained from the third-party payer's perspective and €25,687/QALY gained from the societal perspective. Resulted discounted and undiscounted costs are reported across categories: IPD, vaccine, vaccine administration from two perspectives. The results of SA are reported. Variation of the ICER across the parameters varied in the univariate sensitivity analysis is illustrated by a diagram. The ICER was sensitive to the vaccine effectiveness against NBPP, waning function and incidence of NBPP.

Relevance and validity of economic evaluation

Type of evidence	Question	Rationale	Score
Economic evaluation	Is the study question relevant (choice of comparator,	This study uses a relevant comparator, outcomes and performs analyses from two	**1 ☐ Low relevance/ validity**

		time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	relevant perspectives. The modeled population is a single cohort of eligible for vaccination adults which limits the model outcomes. Due to lack of the German data, application of the clinical and cost-effectiveness studies to inform the model is valid. Where relevant and possible the sources of the German data are included. All relevant costs are included. The inclusion of the indirect effects of the infant vaccination is limited to the projection of the USA data on the effects of the PCV7 infant vaccination. Estimation of incidence of NBPP can be also seen as a limitation. This is based on an assumption that the proportion of NBPP in community-acquired pneumonia cases can be attributed to NBPP similarly to pneumococcal infection.	**2** ☐ **3** ☒ **4** ☐ **High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The modeled population consists of "individuals younger than 60 years of age who were at higher risk of developing IPD diseases ('at-risk adults') and individuals aged 60 years or older ('the elderly')". One cohort of individuals eligible for vaccination with PPSV23 is considered. The population is not divided into age group, but additionally split into immunocompetent and immunosuppressed. The cohort size is obtained from the national statistical data for 2011.	
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates adult vaccination with PPSV23 against IPD and NBPP with revaccination for people <60 years old. Applied coverage rate is based on sales data for PPSV23 due to a lack of publicly available information on the vaccination coverage rate in Germany.	
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The employed model includes five health states: no pneumococcal disease, nonbacteremic pneumococcal pneumonia (NBPP), IPD (including pneumococcal meningitis and bacteremic pneumococcal pneumonia), postmeningitis sequelae (PMS) and death. The model include in indirect effects of vaccinating children via incorporation of time-dependent probabilities of developing IPD. This was based on US data observed during the 7 years following introduction of the PCV7 vaccine in children, the change in the incidence of IPD associated with PCV7 in adults was found to be related to cumulative vaccine uptake in children. Rationale for the approach to the indirect effects is provided.	
4	Comparator	Does the choice of comparators reflect current practice?	The study compares the vaccination to no vaccination scenario which reflects the current practice at the time of the study.	
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The study performs analyses from two perspectives: the third-party payer's perspective and societal perspective. The vaccination costs include vaccine's unit price and vaccine administration costs. The treatment costs of pneumococcal diseases are not further categorized but given for each health state and perspective based on the German data. All costs are estimated in 2010 Euros and the Harmonized Indices of Consumer Prices inflator for healthcare services was used when necessary.	
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	The baseline QALY weights ae obtained from a US cost–effectiveness study assuming no utility decrement for NBPP. For PMS, the utility multipliers used are from a Canadian cost–effectiveness study.	

7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	*Incidence:* The IPD incidence is estimated based on the German surveillance. Indirect effects are modelled as a function of cumulative vaccine coverage rate in children based on the USA data. A cumulative gamma distribution is selected for its goodness of fit. "Coverage rates observed in German children were then used in order to estimate the change in IPD incidence from 2005. A stable incidence was assumed beyond 2012 due to a lack of longer term data." The case–fatality rate was estimated from a Dutch retrospective surveillance study. "It was estimated that approximately 40% of community acquired pneumonia cases were attributable to pneumococcal infection, based on the German Competence Network for Community-Acquired Pneumonia study. Case–fatality rates also came from the Competence Network for Community- Acquired Pneumonia study. Due to a lack of data, a similar incidence of NBPP was assumed across risk groups." Mortality by serotype was estimated based on a Danish nationwide population-based study VE against IPD and NBPP differs between the risk groups but not the ages. The data for VE against IPD for immunocompetent people is taken from a Cochrane systematic literature review and meta-analysis of ten prospective clinical trials [17]; for at-risk immunosuppressed individuals, VE against IPD is obtained from a prospective trial conducted on HIV-infected patients in the USA[19]. VE against NBPP is taken from a prospective cohort study conducted between 2002 and 2005 in Spain[18]. It is assumed that the vaccine does not protect the immunosuppressed patients against NBPP. Approach to the duration of protection is not clearly described.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	Discount rate is 3% for cost and QALY based on the German guidelines on economic evaluations[20]. In SA: 0%, 5%
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	A probabilistic sensitivity analyses (PSA) are performed for the for the following parameters: • Risk of developing IPD • Incidence of IPD • Herd protection effect • Serotype replacement effect • Incidence of nonbacteremic pneumonia across age groups • Case–fatality rates • Relative risk of dying from IPD by serotype • Vaccine effectiveness against IPD • Vaccine effectiveness against NBPP • Waning function of vaccine effectiveness • Administration of PPV23 vaccine • Costs of treatment of IPD and NBPP in- and outpatient • Costs of PMS • Cost per day off • Discount rate • Health related quality of life by age group

			The distributions associated with each model parameter are selected based on the German guidelines on economics evaluations and the published literature. PSA includes 1000 iterations and the cost–effectiveness acceptability curve is plotted.
11	Conclusion	Are conclusions supported by results?	Based on the results the study concludes that that adult PPSV23 vaccination is cost-effective in Germany, due to its broad serotype coverage.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal conjugate vaccine (PCV13) **Setting:** Netherlands			**Study:** Mangen, Marie-Josee J.; Rozenbaum, Mark H.; Huijts, Susanne M.; van Werkhoven, Cornelis H.; Postma, Douwe F.; Atwood, Mark et al. (2015): Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. In The European respiratory journal 46 (5), pp. 1407–1416. DOI: 10.1183/13993003.00325-2015.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	This study reports all the dimensions of the economic evaluation. The reporting can be considered complete and transparent. The information is consistent across the sections of the study. The paper has some gaps about applied age-specific vaccine efficacy and estimation of costs per case, namely applied resources used per case. The aggregated costs per case are given.	**1 ☐ Many gaps/ inconsistent** **2 ☐** **3 ☐** **4 ☒ Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The target population is defined as consisting of five age cohorts (18–49, 50–64, 65–74, 75–84 and ⩾85 y.o.) of 2012, Netherlands. Three health risk groups for pneumococcal diseases are considered: low-, medium- and high-risk groups. The comorbidities which are attributable to the medium- and high-risk state as well as the proportion of people belonging to these groups (for each age cohort) are listed in the supplemental material.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: “vaccination of adults aged 65–74 years with a single dose of PCV13 administered at the start”. Vaccination coverage: 63.9% for low risk groups; 81.5% for medium- and high risk groups	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The study applies a probabilistic Markov-type model with a 1-year cycle length. The structure is illustrated in the supplemental material with a schematic representation without attribution of costs and transition probabilities.	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The vaccination with PCV13 is compared to no vaccination. Rationale is stated.	
5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis is performed from a societal perspective. Rationale is not given. The healthcare payer perspective is considered in	

			SA.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	Cost-effectiveness analysis of elderly vaccination with PCV13 compared to no vaccination. The outcomes of the analyses are estimated incidences of IPD, inpatient CAP, outpatient CAP, deaths, costs, life years and QALYs. Cost-effectiveness is estimated as cost per QALY gained and cost per LYG. "In 2012, the Dutch gross domestic product (GDP) per CAPITA was €35 300. A strategy is considered highly cost-effective if ICER is <1×GDP per CAPITA and cost-effective if ICER is <3×GDP per CAPITA."
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence* In the supplemental material the following model input parameters are provided: • Incidence of IPD stratified by age- and risk-group • Incidence of inpatient CAP stratified by age- and risk-group • Incidence of outpatient CAP stratified by age- and risk-group • Serotype (PCV13 and nonPCV13) distribution of IPD stratified by age-group *Vaccine-related parameters* The authors base the calculations on the CAPITA trial. The study does not contain explicit numbers for age-specific VE. The supplemental material gives a plot where it is shown that the VE would deteriorate and VE would be lower for the higher ages. For CAP: the age at which the predicted efficacy equaled the VE from the CAPITA-trial (45.56%) was 76.2 years *Waning immunity* The following assumptions are made: • stable during the first 5 years following vaccination • afterwards: wane annually at a rate of 5% during years 6–10 • wane 10% annually during years 11–15 • no efficacy was assumed from year 16 onwards We calculated years of full protection and average duration of protection with PCV13 against IPD: Years of full protection (Average duration of protection): ag IPD: 12.2y (10.6y for 65y.o, 9.7y for 73 y.o, 8.5 y for 80.y.o) Ag non-IPD: 12.2y (7.9 y for 65y.o, 6.1y for 73 y.o, 4.9 y for 80.y.o) *Coverage:* • is stratified by age- and risk-group • 63.9% for low risk groups • 81.5% for medium- and high risk groups *Costs* A full list of included unit cost prices is provided (2012 €) in the supplemental material Aggregating categories of the unit cost prices are : • Direct healthcare costs • Direct non-healthcare costs • Indirect non-healthcare costs The utilization of resources per case is not provided. Applied aggregated costs per case (direct healthcare costs and indirect non-healthcare costs) are given for IPD, inpatient- and outpatient CAP for the "survivor" and "fatal" outcomes. The values are stratified by age- and risk-group and expressed in 2012 euros. *Utility estimates* in the Dutch general population, age stratified

8	Time horizon	Is the time horizon reported?	The costs, life years, and QALYs are calculated over the lifetime of the cohort.
9	Discount rate	Is the discount rate reported?	Discount rate is reported: Costs: 4% ; Health benefits: 1.5%
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	The following SA are reported: • Univariate sensitivity analyses: each parameter is varied separately by 25% (increasing/decreasing) • Multiway sensitivity analyses • An additional scenario to test the impact of herd protection on ICER: "by decreasing the proportion of PCV13 serotypes for IPD and CAP with 0% (base-case) up to 90%, with herd effects remaining stable from year 1 onwards." The ranges of the parameters are reported with the made assumptions.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	The results are reported for the baseline analyses and sensitivity analyses. ICERs for the evaluated vaccination strategies are graphically represented. The incidence over the modeled time horizon for IPD, inpatient CAP and outpatient CAP as well as aggregated direct- and indirect healthcare costs, vaccination costs and net societal costs are reported in the supplemental material. The results of SA are presented in the table in the supplement and as a tornado diagram in the main text. Base case ICER: €8650 per QALY (95% CI 5750–17 100) gained; €7650 per LYG (95% CI 5300–12450).

Relevance and validity of economic evaluation

Type of evidence	**Question**	**Rationale**	**Score**
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	This study evaluates adult vaccination with PCV13 against IPD, inpatient CAP and outpatient CAP. Chosen population, comparator, perspective, time horizon, discount rates, costs and health outcomes are relevant. The analysis is performed from a societal perspective. Variable vaccination strategies are compared with no vaccination scenario. A model of Markov type was developed with states reflecting the considered diseases. Vaccine efficacy was obtained from CAPITA trial. Epidemiological - and cost data applied in the study were obtained from national sources. It was assumed that there were no indirect effects of PCV10 childhood vaccination based on epidemiological data. The effects of PCV7 childhood vaccination were stated to be reflected in the applied incidence data. However, it is not really clear from the source that IPD does not decline or reached plateau: none of the serotypes shows signs stopped declining or are plateauing as depicted in Figure 2 of Knol et al[21].	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☒** **4 ☐ High relevance/validity**

	Dimension	**Question**	**Comment**
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The study considers an adult population. The division of the population into age cohorts and risk groups is based on the Dutch data. Demographics: national statistics of 2012. Division in the risk groups is based on "the prevalence of clinical risk factors from electronic medical records in a large network of general practitioners (GPs) in the Netherlands". Three health risk groups for pneumococcal diseases are considered: low-, medium- and high-risk groups. The prevalence of the listed clinical risk factors is described in the supplemental material and the estimation is based on the defined risk-groups for influenza vaccination by the Dutch Health Council.

2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates adult pneumococcal vaccination against IPD, inpatient – and outpatient CAP. 12 evaluated vaccination strategies vary in the age range of eligibility and the group of pneumococcal disease risk: Base-case (65-74-all), 65-74-low, 65-74-medium, 65-74-high, 65-74-at risk, 65plus-at risk, 65plus-all, 50plus-at risk, 50plus-all, 18plus-at risk,50plus-all &18-49-at risk and 65plus-all&18-64-at risk. Coverage rates are based on observed rates in the regional influenza vaccination program.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The following events are included into the structure: IPD, CAP inpatient, CAP outpatient, death. These disease states are modeled for each health risk, where the subjects can transit to the state of higher risk than the current state. Transition to the disease states are influenced by vaccination effects and herd protection stemming from the childhood vaccination with PCV10.
4	Comparator	Does the choice of comparators reflect current practice?	The vaccination with PCV13 is compared to no vaccination. Current practice states that there is no other universal adult pneumococcal vaccination. Vaccine coverage is assumed based on the data from the "Dutch influenza vaccination coverage among those aged ⩾65 years in 2012".
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The analysis is performed from a societal perspective and the healthcare payer perspective is evaluated in SA. The direct healthcare costs contain all relevant costs. "Costs were estimated by multiplying resources used, as extracted from different studies with their corresponding unit cost prices". Although, the study reports a broad list of prices per unit of healthcare services and diagnostics, it does not provide the disease specific resource utilization. "Direct healthcare and non-healthcare costs were considered to start at symptom onset or first contact with the healthcare system up to a maximum 28 days or until recovery for outpatient CAP, and up to 1 month post-discharge for IPD and inpatient CAP survivors." "All costs are expressed in 2012 Euros"
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	Utility estimates in the Dutch general population are reported. QALY loss due to IPD, inpatient CAP and outpatient CAP are given.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	The age- and risk-group specific incidence and case fatality rates of IPD are estimated from the national surveillance data of 2014. Methods are not described. Vaccination coverage rates are obtained from the Dutch National Influenza Prevention Program *Incidence, stratified by age- and risk-groups:* • IPD incidence and serotype distribution of IPD are derived from the Dutch surveillance data ("June 1,2012 to May 31, 2014") • Inpatient CAP incidence is obtained from radiography-confirmed CAP admissions in a "cluster-randomized-cross- over trial in seven Dutch hospitals (CAP-START trial, from February 2011 to January 2014)", "with adjustment for coverage (i.e. proportion of International Classification of Diseases, 9th revision codes 480–486 in the CAP-START hospitals compared to the total Dutch population, using Dutch hospital data)". • Case-fatality rates of inpatient CAP are obtained from the CAPITA and CAP-START trials. • Incidence of outpatient CAP is obtained from a "database containing anonymous routine healthcare data from the digital patient records of 45 GP practices (160 GPs, full time and part time) in Utrecht and its vicinity (Julius GP Network)". "Incidence rates were multiplied by 0.57 to adjust for the proportion not confirmed using radiography". *Indirect effects of PCV10 childhood vaccination:* The study assumes that there are no net indirect effects of infant PCV10 vaccination for adults. The effects of its precursor

			PCV7 are reflected in the applied incidence data and "herd effects were assumed to be fully present at the time of initiation of PCV13 vaccination". These assumptions are made based on a published study which provides serotype-specific incidences based on sentinel surveillance data, however, it is not really clear from the source that IPD incidence does not decline or has reached a plateau. *Vaccine-related parameters* The study applied the vaccine efficacy data from the CAPITA trial. Age-specific VE is illustrated in a plot. It does not allow assessing the applied age effects of VE. Duration of PCV13-protection is applied based on assumptions. Other parameters are obtained from national data sources.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	Discount rates are applied in accordance with Dutch guidelines.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	The uncertainty of the following parameters are tested in multiway SA: case-fatality rates, vaccine effectivity, waning immunity, changes in vaccination coverage, discount rates, general utilities, perspective and vaccination costs.
11	Conclusion	Are conclusions supported by results?	Based on the defined cost-effectiveness threshold, all strategies of PCV13 (except PCV13 vaccination of only low-risk patients aged 65–74 years) are considered highly cost-effective in the Netherlands.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)			
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** Belgium		**Study:** Blommaert, Adriaan; Bilcke, Joke; Willem, Lander; Verhaegen, Jan; Goossens, Herman; Beutels, Philippe (2016): The cost-effectiveness of pneumococcal vaccination in healthy adults over 50: An exploration of influential factors for Belgium. In Vaccine 34 (18), pp. 2106–2112. DOI: 10.1016/j.vaccine.2016.03.003.	
Completeness and consistency of reporting economic evaluation			
Type of evidence	**Question**	**Rationale**	**Score**
Economic evaluation	Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)?	This study reports all the dimensions of the economic evaluation. The reporting can be considered complete and transparent. The information is consistent across the sections of the study. The paper has some gaps about the exponential waning of the vaccine effectiveness applied in SA. Applied indirect effects are described with provision of the respective parameters.	**1 ☐ Many gaps/ inconsistent** **2 ☐** **3 ☐** **4 ☒ Complete and consistent**

		See dimensions below		
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The modeled population is age-stratified (by single year of age between 50 and 90) and consists of multiple cohorts of general adult population. The population is not stratified by health risk groups.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: adult pneumococcal conjugate vaccination against IPD and non-IPD. The study evaluates the following vaccination strategies: • vaccination with PCV13 • vaccination with PPSV23 • addition of PCV13 vaccination to PPSV23 Coverage is 75%	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The developed model is age-structured, static and multi-cohort. The model tracks for the cohorts the costs and effects of the vaccination. The description and the structure of the model as a scheme are given in the supplement. The transition parameters are assigned and described. IPD include bacteremic hospitalised pneumonia, septicaemia and meningitis Non-IPD include outpatient pneumonia and non-bacteremic hospitalised pneumonia	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The study uses the following comparators: • vaccinations with PCV13 and PPSV23 are compared to no vaccination • addition of PCV13 vaccination to PPSV23 is compared to vaccination with PPSV23	
5	Perspective	Are the perspective of analysis and its rationale stated?	The study uses a health care payer's perspective. The rationale is given. No other perspective is considered in SA.	
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	This study conducts a cost-effectiveness analysis of adult vaccination against IPD and non-IPD. Three options are compared: vaccination with only PPSV23, vaccination only with PCV13 and addition of PCV13 to the vaccination with PPSV23. The health outcomes are expressed in quality-adjusted life years. The conclusion about the cost-effectiveness is made based on cost /QALY gained threshold of 35,000 Euro. The study also investigates effects of vaccine prices, indirect effects of pediatric vaccination and duration of the vaccine protection on the cost-effectiveness estimates.	
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* The age- and cohort-specific proportion of people under the risk of development IPD and non-IPD i.e. not vaccine protected, is calculated using the following parameters: vaccination coverage, vaccine effectiveness, age dependent and serotype group-specific initial (prior vaccination) incidence and the serotype specific incidence factor that reflects the incidence changes due to the pediatric vaccination with PCV13 (as a cohort- and serotype group-specific ratio of observed- to the initial incidence). The numbers of IPD or non-IPD cases per year are calculated using the disease-specific hospitalization rates which are provided with the respective references. Due to limitations of the Belgian data, the incidence for bacteremic pneumonia (BP) and non-bacteremic pneumonia (NBP) are calculated based on assumptions which are tested in SA: age-independent proportion BP and case-fatality are equal for BP and NBP. Case-fatality rates are given for each disease. Probabilities of complications after meningitis (bilateral hearing loss and neurological sequelae) are given with the references. Serotypes are divided into four groups: (PPSV23-PCV13)-type, (PCV13-PPSV23)-type, “both” (in both vaccines), non-	

			vaccine-type *Indirect effects:* Indirect impact of the pediatric vaccinations with PCV7 and PCV13 on the incidence among adults consists of herd immunity and replacement effects. These are incorporated into computation of the proportion of vaccine unprotected people who may develop IPD or non-IPD. The factor is serotype-group specific and incorporated based on assumptions which are described in the main text and obtained from the data from England and Wales. *Vaccine-related parameters* Vaccine efficacies are assumed to be age independent PCV13 against IPD: 75% PCV13 against NBP: 41.1% PPSV23 against IPD: 55% PPSV23 against NBP: 0% Waning rate: Made assumptions are the same for both considered vaccines: 5 years of full protection than instant drop to zero. Waning varies in SA: (i) constant protection over time period between 4 and 15 years, and (ii) 5 years of full protection followed by an exponential decay (half-life varies between 0-10 years). *Health outcomes:* Average QALY loss decrement: disease- and age-group-stratified. *Costs:* • Vaccine administration cost per dose is given. • Hospitalization costs: age- and IPD-stratified. • Non-age specific medical cost for outpatient pneumonia • Year 2014
8	Time horizon	Is the time horizon reported?	The time horizon is stated and is lifetime: every age cohort is followed to death.
9	Discount rate	Is the discount rate reported?	Discount rate is reported: Costs: 3%; Health outcomes: 1.5%
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Sensitivity analyses are performed for vaccination with PCV13 or PPSV23 versus no vaccination and for vaccination with PCV13 and PPV23 versus the vaccination with PPSV23 alone. SA are performed to test the duration of VE, the indirect effects of the pediatric vaccination and "the proportion of outpatient pneumonia cases caused by pneumococcus and of non-bacteremic hospitalized pneumonia". The ranges are reported.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	The results are reported for the baseline analyses and sensitivity analyses. The results include "incremental effects, direct medical costs, vaccination costs, quality-adjusted life-years and incremental cost-effectiveness ratios vs no vaccination" for vaccination of different age groups (50-64,64-75,75+y.o.) under the assumptions of equal uptake (75%) and duration of effectiveness for PPSV23 and PCV13 (5 years).

			Reported ICER: PCV13 vs no vaccination (EUR/QALY, discounted) "presented as median (mean)" of 1000 simulations 50-64y.o. 232,352 (218,774) 64-74y.o. 106,399 (99,620) 75+ y.o. 72,556 (67,507) PPSV23 vs no vaccination (EUR/QALY, discounted) "presented as median (mean)" of 1000 simulations 50-64y.o. 130,051 (128,859) 64-74y.o. 67,791 (67,182) 75+ y.o. 50,263 (49,760)

Relevance and validity of economic evaluation

Type of evidence	**Question**	**Rationale**	**Score**
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	This study evaluates scenarios of the introduction of PCV13 for the adult vaccination against invasive and non-invasive pneumococcal diseases. The study uses the relevant comparators providing the analyses in comparison with the current vaccination practice and no vaccination. The age structure of the modeled population complies with the targeted population for the intervention, however, the population is not risk-stratified. The vaccine effectiveness for PCV13 is obtained from the data of the CAPITA trial. Epidemiological - and cost data applied in the study are obtained from the national sources. The applied perspective, time horizon, discount rates, costs and health outcomes are relevant. The study applies possible herd effects of the pediatric vaccination with PCV13 based on the projections of the effects of the PCV7 vaccination observed in children. The replacement effects are applied based on assumptions. The study examines the effects of the uncertainty around the duration of the vaccine protection and indirect effects of the pediatric vaccination as well as around the incidence of non-bacteremic hospitalized pneumonia on the cost-effectiveness estimates.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☐** **4 ☒ High relevance/validity**

	Dimension	**Question**	**Comment**
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The population size for each modeled age in years is based on the national data for 2014.
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates adult pneumococcal vaccination against IPD and non-IPD. The evaluated vaccination strategies vary in the age range of eligibility and the applied vaccine. Vaccine coverage is based on the influenza vaccination in the elderly in Belgium.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	Each modeled age and cohort is followed from the vaccination point to the "death of the last survivor." The model includes calculation of the age- and cohort-specific proportion of the population at risk of development IPD or non-IPD. This is governed the vaccination coverage, vaccine effectiveness and the incidence. Vaccine effectiveness and incidence are stratified by the four serotype groups. For the population at risk the model includes the following events: development of

			IPD (bacteremic hospitalised pneumonia, septicaemia and meningitis) or non-IPD, and disease-related death (governed by the case-fatality rates). In the case of meningitis the model includes development of disability: hearing problems or neurological sequelae. The model simulates costs and effects of pneumococcal vaccination programs. The model is static and does not include the transmission process.
4	Comparator	Does the choice of comparators reflect current practice?	The analysis is performed in comparison to no vaccination and the vaccination with one dose of PPSV23 (the current recommendation the Superior Health Council in Belgium).
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The perspective is of health care payer. Cost data are obtained from a survey of the Belgian population (published in 2006). The reported costs are categorized into hospitalization costs, which aggregated various costs categories (listed in the supplement), and medical cost for the patients with outpatient pneumonia. All costs are expressed in 2014 Euros.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	The incremental QALY losses due to IPD and non-IPD are age specific. Average QALY loss decrements are obtained from a published study by Melegaro et al[22]. These are multiplied "by the ratio of the average age specific health related quality of life in Belgium and the adult population's average health related quality of life in Belgium".
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	*Incidence:* Serotype coverage is obtained from "the Belgian pneumococcal reference centre for the period 2012-2014". Assuming same serotype distribution for both IPD and non-IPD cases. Initial incidence at the start of the vaccination program is obtained from the National reference centre. The herd immunity effects are incorporated into the model by a projection of the effects of the PCV7 vaccination observed among children ("2–4 year olds over the period 2003–2008") in Belgium. The herd effects are modelled as an annual decline of 24% in circulating PCV13-type serotypes ("varied from 0 over 12% to 24%"). Serotype replacement effects are modeled as "compensation of this PCV13 incidence reduction" due to herd effects. The following values are applied: 0%, 50% and 100% replacement. Case-fatality rates, all-cause death rate, life expectancy and disease-specific hospitalization rates are obtained from the national data sources. *Vaccine effectiveness:* The VE effectiveness parameter for PCV13 is obtained from the CAPITA trial. The VE effectiveness parameter for PPSV23 is obtained from a systematic literature review by Moberley et al[17].
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	The applied discount rates are in accordance with the Belgian guidelines for economic evaluations and budget impact analyses: • Life-years and QALYs: an annual rate of 1.5% • Costs: an annual rate of 3%

10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	In the sensitivity analyses for PCV13 or PPSV23 versus no vaccination the uncertainty of the following parameters is tested: • duration of vaccine efficacy • reduction in PCV13-type serotype incidence The duration of the VE is varied in two scenarios of waning: • no waning over the assumed period of vaccine protection which is also varied between 4 and 15 years • exponential waning: "assumed 5 years of no waning (period of complete vaccine protection) followed by an exponential decay with its half-life varied between 0 and 10 years" Impact of herd effects is varied as 0%, 12% and 24% reduction in PCV13-type incidence. Replacement effects variation is 0%,50%,100%. A particular focus is placed on influence of the vaccine duration of the maximum vaccine price so that the vaccination is cost-effective vs no vaccination at the threshold of 35,000 Euro/QALY. In the sensitivity analysis for adding PCV13 to PPSV23 versus PPV23 alone the uncertainty of "the proportion of outpatient pneumonia cases caused by pneumococcus and of non-bacteremic hospitalized pneumonia" is tested. Other input parameters are given with confidence intervals or a distribution applied in the simulations. Ranges are plausible.
11	Conclusion	Are conclusions supported by results?	Based on the results the study concludes that the adult vaccination with PCV13 is unlikely to be cost-effective in Belgium. Vaccinations with PPSV23 dominate vaccinations with PCV13 or addition of PCV13 to PPSV23 comparing to no vaccination. The authors point out that the difference in the cost-effectiveness between vaccinations with PCV13 and PPSV23 is caused by the large vaccine price difference.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)			
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** Spain		**Study:** Rodriguez Gonzalez-Moro, Jose Miguel; Menendez, Rosario; Campins, Magda; Lwoff, Nadia; Oyaguez, Itziar; Echave, Maria et al. (2016): Cost Effectiveness of the 13-Valent Pneumococcal Conjugated Vaccination Program in Chronic Obstructive Pulmonary Disease Patients Aged 50+ Years in Spain https://www.sciencedirect.com/science/article/pii/S0264410X16002814?via%3Dihubate Vaccination Program in Chronic Obstructive Pulmonary Disease Patients Aged 50+ Years in Spain. In Clinical drug investigation 36 (1), pp. 41–53. DOI: 10.1007/s40261-015-0345-z.	
Completeness and consistency of reporting economic evaluation			
Type of evidence	**Question**	**Rationale**	**Score**
Economic evaluation	Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results,	This study reports all the dimensions of the economic evaluation. The reporting can be considered partly complete and transparent. The paper has gaps in reporting the rationale for the applied methods to incorporate herd effects and applied categories of the healthcare costs.	**1 ☐ Many gaps/ inconsistent** **2 ☐** **3 ☒** **4 ☐ Complete and consistent**

		discussion)? *See dimensions below*		
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The target population is described and defined as individuals with chronic obstructive pulmonary disease (COPD) ≥ 50 years old.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: single dose of PCV13 against IPD and all-cause NBP at model entry.	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	Model is of the Markov type. The states are named. The structure of the model is illustrated in a figure without assigning respective costs and transition states. Coverage is 59.5 % (both vaccinations) of COPD patients ≥ 50 years old.	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	Comparator is vaccination with a single dose of PPSV23 at model entry.	
5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis is performed from the perspective of the Spanish National Healthcare System. The rationale for the selection is not given. The perspective is not varied in SA.	
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The study provides a CEA. Results are given in ICER. The outcomes used are QALYs.	
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* Herd protection from the pediatric vaccination is reported. The rationale for applied effects is not given. Age group specific incidence rates are provided for IPD, inpatient NBP and outpatient NBP. The sources are stated. Age group-specific mortality rates are given for general population, IPD, and inpatient IPD. The sources are stated. *Vaccination related parameters:* *Vaccine effectiveness* parameter is age-specific and sated as: PCV13 against IPD: 50-64y.o.: 82.0% 65-74y.o.: 76.8% 75-84y.o.:: 72.2% >85y.o.: 67.6% PCV13 against inpatient NBP: 50-64y.o.: 9.5% 65-74y.o.: 8.9% 75-84y.o.: 8.4% >85y.o.: 7.9% PCV13 against outpatient NBP: 50-64y.o.: 9.5% 65-74y.o.: 8.9% 75-84y.o.: 8.4% >85y.o.: 7.9% PPSV23 against IPD: 50-64y.o.: 87.3% 65-74y.o.: 76.6% 75-84y.o.: 67.8% >85y.o.: 59.4% PPSV23 against inpatient NBP: 0% PPSV23 against outpatient NBP: 0%	

			Sources are given. *Waning rate:* Vaccine efficacy by years since vaccination is given for all age groups and vaccines for the years: 1-5, 6-10,11-15, >15. We calculated years of full protection and average duration of protection with PPSV23 against IPD: Years of full protection (Average duration of protection in years): PCV13 against IPD: 50-64y.o.: 9.7 (8.0) 65-74y.o.:8.6 (6.6) 75-84y.o.:7.1 (5.1) >85y.o.:4.7 (3.2) PCV13 against NBP: 50-64y.o.: 9.7 (0.9) 65-74y.o.:8.6 (0.8) 75-84y.o.:7.1 (0.6) >85y.o.:4.7 (0.4) PPSV23 against IPD: 50-64y.o.: 5.1 (4.9) 65-74y.o.:3.2 (3.6) 75-84y.o.:7.1 (2.6) >85y.o.:4.7 (1.7) *Healthcare costs* Attributed costs and the used sources are described. The study gives unit cost per vaccine and aggregated management disease cost per case of IPD, inpatient NBP and outpatient NBP. *Utilities:* Utilities are given for the COPD general population along with the utility reduction due to disease.
8	Time horizon	Is the time horizon reported?	Time horizon is reported and is lifetime in the baseline. In SA the modeled time horizon is varied: 5, 10, 20 years.
9	Discount rate	Is the discount rate reported?	The discount rate is reported. In the base case the applied discount rate is 3% for both costs and QALY. In SA: undiscounted and 5% for both costs and QALY.
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	A probabilistic sensitivity analysis and a one-way deterministic sensitivity analysis are performed. Rationale for the distribution and its parameterization is not provided.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	The resulted ICERs, total costs, QALYs and LYG are listed per age group. Overall, ICER is €1,245 per additional LYG and €1,844 per QALY gained compared to vaccination with PPSV23. The results of SA are also given in a tornado diagram.

Relevance and validity of economic evaluation

Type of evidence	Question	Rationale	Score
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	This study provides a cost-effectiveness analysis of vaccinating adults with COPD aged ≥50 years. The model structure, assumptions about the time horizon, discount rates and vaccine waning rates are considered reasonable. The analysis is performed from the perspective of the National Healthcare System and the considered costs are limited to the direct costs per case of the disease. The evaluated vaccination strategy is limited to vaccinating individuals with COPD. This vaccination strategy is compared with the current vaccination program with PPSV23 which is recommended for immunocompromised patients and those with chronic diseases. The study models a cohort of COPD patients and assumes that the patients are immunocompetent. PCV13 VE is obtained from CAPITA trial. IPD incidence is obtained from a study conducted in	**1 ☐ Low relevance/ validity** **2 ☒** **3 ☐** **4 ☐ High relevance/validity**

			England. Modelling of the herd effects of the pediatric vaccination with PCV13 are not described making it difficult to assess its plausibility. The sensitivity analyses are performed for the critical parameters.	
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The study models an age-stratified cohort of patients ≥50 years old with COPD. No other comorbidities are stated. Age groups are 50–64, 65–74, 75–84, and ≥85 years. The population size is based on the statistics from the Spanish National Statistical Institute. The number of COPD patients is obtained from a Spanish published study which considers prevalence of COPD in Spain. The PCV13 vaccine efficacy is obtained from the CAPITA trial. The population of the trial does not include exclusively patients with COPD.	
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates vaccinating adult COPD patients with a single dose of PCV13 against IPD and all- cause NBP. The coverage is obtained from the Spanish National Health Survey of 2011/2012.	
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The model is of Markov structure and includes the following states: alive without IPD or all-cause NBP; alive with IPD; alive with all-cause inpatient NBP; alive with all-cause outpatient NBP; and death. It is assumed that the modeled individuals enter the model in the non-PD state and without being previously vaccinated and receive a single dose of the respective vaccine at the model entry.	
4	Comparator	Does the choice of comparators reflect current practice?	The comparator is the current vaccination with a single dose of PPSV23. The study does not compare both vaccinations with no vaccination scenario. The study does not consider revaccination with PPSV23. The rationale is not given.	
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The study assumes a third-party payer perspective. The costs contain only direct healthcare costs. The data for aggregated disease management costs is obtained from published studies considering Spain. All costs are given in euros and adjusted to 2015 prices. The vaccine costs are estimated based on the pharmacy retail prices “adjusted with a 7.5 % mandatory deduction”.	
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	Due to lack of the Spanish data, the stated health-state utilities for the COPD general population are obtained from published cost-effectiveness analyses conducted for USA and England. The utilities are age stratified.	
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	*Age-specific incidence:* Herd protection from the pediatric vaccination is given in percentages. Age stratified percentages represent maximum reduction in disease due to PCV13 vaccination. In the modeled year 5 and the following years of the time horizon the herd effects are assumed to achieve this maximum. The values of the maximum reduction in IPD due to herd effects are obtained from the Spanish National Health Survey 2011/2012. Those for NBP are obtained from published studies. The rationale is not given. The methods are not stated. There is not enough data to assess the used approach for modelling of herd effects. Age group specific IPD incidence and case-fatality rates are obtained from a published study looking at clinical conditions	

			causing risk of IPD development conducted in England[23]. The incidence of inpatient NBP is obtained from a Spanish database of hospitalizations in 2012. The incidence of outpatient NBP is estimated as a percentage of total all-cause NBP (58.5 %). The estimate is based on a retrospective epidemiological study conducted Badalona (Barcelona, Spain). It is not stated whether the incidence rates are obtained for COPD patients or for a general population. The methods are not described. All-cause mortality rates for COPD population are obtained from the Spanish National Statistical Institute. The inpatient NBP-related mortality is obtained from a published Spanish study looking at the patients with pneumonia and chronic obstructive pulmonary disease. *Vaccine Efficacy:* The study assumes that the COPD patients are "at risk but immunocompetent individuals". The parameters for the age-specific PCV13 vaccine efficacy against IPD and all-cause NBP are obtained from the CAPITA trial. The parameters for the age-specific PPSV23 vaccine efficacy against IPD is obtained froth the study by Andrews t al[13]. The VE of PPSV23 is assumed to be zero. Age-specific waning rates are applied as VE for the years after the initial vaccination based on assumptions.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	The discount rate is applied in accordance with the Spanish recommendations for development of economic evaluations.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	In the probabilistic SA the uncertainty of the following parameters is tested: age-specific incidence rates and case-fatality rates for IPD (Beta distributions), inpatient- and outpatient NBP; costs per disease case (Log-normal distributions); indirect effects, utilities and disease-related disutility (uniform distributions for these parameters). The parameters of the respective distributions are provided without a description or a rational making plausibility difficult to assess. In the one-way deterministic SA the following parameters are varied: time horizon, discount rate, revaccination at 5 years for 56.4 % with current vaccination policy, vaccination coverage, waning effect, utility values, vaccine effectiveness, disease incidences, mortality and the reduction of the vaccine price for both PPV23 and PCV13. The results of SA indicate that the indirect effects are improperly modeled.
11	Conclusion	Are conclusions supported by results?	Conclusion: Based on the threshold of 30,000 Euro/QALY ("accepted Spanish cost-effectiveness threshold") the PCV13 vaccination of COPD patients aged ≥50 years is considered to be cost-effective. The results show a lower ICER (vs. the current vaccination with PPSV23) than the considered threshold.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** USA			**Study:** Stoecker, Charles; Kim, Lindsay; Gierke, Ryan; Pilishvili, Tamara (2016): Incremental Cost-Effectiveness of 13-valent Pneumococcal Conjugate Vaccine for Adults Age 50 Years and Older in the United States. In Journal of general internal medicine 31 (8), pp. 901–908. DOI: 10.1007/s11606-016-3651-0.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	This study reports all the dimensions of the economic evaluation. The reporting can be considered complete and transparent. The information is consistent across the sections of the study. The paper has minor gaps about the waning rate of age-specific vaccine efficacy and estimation of costs per case, namely applied resources used per case. The aggregated costs per case are given. Methods for applying indirect effects are described with provision of the respective parameters and data	**1** ☐ **Many gaps/ inconsistent** **2** ☐ **3** ☒ **4** ☐ **Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The modeled population is reported. It consists of immunocompetent adults in three cohorts: 50-year-olds, 60-year-olds, 65-year-olds. The sizes of the initial cohorts are given. From these immunocompromised individuals are subtracted. The rational is given. The final size of the population is not stated. The immunocompetent population is risk-stratified: healthy and high-risk. The clinical conditions for the stratification are given. The proportions of people belonging to these groups are not listed.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: vaccinating adult population with PCV13 against IPD and non-bacteremic pneumococcal pneumonia. The following strategies are evaluated: • addition of PCV13 to existing PPSV23 recommendation at ages 50, 60, or 65 years • replacement PPSV23 at age 65 with PCV13 at age 65	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The study applies a probabilistic model with Monte Carlo simulations. The model structure is illustrated in a figure with assigned arms and schedules.	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The vaccination strategies are compared to the current vaccination practice: “a dose of PPSV23 at diagnosis of high-risk condition for ages 50–64, followed by a dose of PPSV23 at age 65 (or 5 years later)”.	
5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis is conducted from a societal perspective. No other perspectives are considered.	
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	This is a cost-effectiveness analysis of adult vaccination with PCV13 compared to current vaccination practice. The outcomes of the analyses are: new disease incidence, deaths, medical and non-medical costs, QALYs.	

7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* The serotypes are classified as PCV13-type, PPSV23-type, (PPSV23-PCV13)-type and nonvaccine serotypes. The following parameters are provided with the respective sources: • The IPD incidence rates by the serotype group across the age groups and risk groups. • The inpatient and outpatient NBP incidence rates across the age- and risk groups. • Proportion of the NBP due to the PCV13 serotypes • The case-fatality rates for IPD and NBP All-cause mortality is not provided. The methods of inclusion indirect effects of pediatric vaccination with PCV13 are described and the parameters are stated. *Vaccine-related parameters* The vaccine effectiveness is not age- or risk group specific. The sources are given. PCV13 against IPD: 50-64y.o.: 75% ≥65y.o.:75% PCV13 against NBP: 50-64y.o.: 45% ≥65y.o.:45% PPSV23 against IPD: 50-64y.o.: 74% ≥65y.o.:74% PPSV23 against NBP: 0% Waning immunity: The following assumptions are made for PCV13: • "no declines in effectiveness between the ages of 50 and 65". • after age 65 the waning rate of 10% every 5 years The following assumptions are made for PPSV23: • Linear waning by 5 years increment: 1-5 years after the initial vaccination down to 50%, 6-10 down to 30% and 11-15 down to 0% of initial effectiveness. The slopes are not given. Due to lack of data we could not calculate years of full protection and average duration of protection Coverage rates: Coverage rates are given for age- and health risk group: over age 65 - 59.9 % high-risk 50–64-year-olds - 20 % *Costs* Age- and risk group stratified aggregated costs are given per case of IPD, inpatient NBP and outpatient NBP. Vaccine price is stated and is a government contract vaccine *Health outcomes:* Quality-adjusted life year decrements are described.
8	Time horizon	Is the time horizon reported?	The costs and health outcomes are calculated over lifetime or until age 100.
9	Discount rate	Is the discount rate reported?	Reported : Costs and outcomes: 3%

10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	The following SAs are reported: • multivariate SA, ranges are given • one-way sensitivity analyses • a scenario with more rapid waning of PCV13 • a scenario with PPSV23 effectiveness against NBP is 45% (analogously to PCV13)
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	The results are reported for all evaluates strategies in the baseline analyses and sensitivity analyses. The resulted costs consist of total, medical and vaccine costs. In the base case the ICERs (95% CI) are: • addition of PCV13 to existing PPSV23 recommendation at age 50 years: 333,200 (159,370, 431,171) $/QALY • addition of PCV13 to existing PPSV23 recommendation at age 60 years: 238,227 (131,641, 355,424) $/QALY • addition of PCV13 to existing PPSV23 recommendation at age 65 years: 62,065 (26,951, 147,828) $/QALY • replacement PPSV23 at age 65 with PCV13 at age 65: 46,396 (cost-saving, 509,987) $/QALY

Relevance and validity of economic evaluation

Type of evidence	**Question**	**Rationale**	**Score**
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	This study uses a relevant population, comparator, time horizon, outcomes and perspective. The population is divided into three age cohorts and consists of the healthy individuals. The comparator is the current recommendation. The vaccine effectiveness estimates are obtained from the relevant sources: CAPITA trial for PCV13 and systematic literature reviews for PPSV23. The study includes serotype division and gives respective incidence rates. The rates are based on the national data. The indirect effects of the pediatric vaccination with PCV13 are incorporated as changes in the serotype specific incidence based on the national surveillance data. The study includes not age-stratified disease-specific QALY decrements.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☒** **4 ☐ High relevance/validity**

	Dimension	**Question**	**Comment**
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The sizes of the modelled three age-cohorts are defined by the United States population of 2013. The immunocompromised individuals are excluded from the analysis due to "this group was recommended to receive PCV13 in 2012 and the cost effectiveness of that recommendation has already been evaluated in previous work". The modelled population corresponds to the CAPITA trial, the data of which are used for PCV13 effectiveness estimate.
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates pneumococcal vaccination against IPD, inpatient – and outpatient NBP for adult immunocompetent population. Evaluated vaccination strategies vary in the age range of eligibility, the group of pneumococcal disease risk and the applied vaccine. The coverage rates are based on the based on the US National Health Interview Survey of 2012.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The developed model computes disease cases and deaths due to invasive pneumococcal disease (IPD) and nonbacteremic pneumococcal pneumonia (NBP). The model tracks the assigned costs. The following events are included into the structure: vaccination schedule and vaccination status, IPD, NBP (inpatient- and

			outpatient visit), death from pneumococcal diseases.
4	Comparator	Does the choice of comparators reflect current practice?	Different vaccination strategies are compared to the vaccination of the current recommendation: “a dose of PPSV23 at diagnosis of high-risk condition for ages 50–64, followed by a dose of PPSV23 at age 65 (or 5 years later).”
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The analysis is performed from a societal perspective. There is no variation in the perspective in SA. The reported costs are aggregated as cost per case for each considered disease making it difficult to conclude whether all relevant costs are included. The cost data are obtained from the national sources: “paid health insurance claims from the Truven Health Analytics MarketScan database 2010”. Vaccine costs are based on published government contract vaccine prices of 2013 ($85.189). All costs are expressed in 2013 US dollars.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	The applied QALY decrements for inpatient- and outpatient NBP are obtained from a published cost-effectiveness analysis conducted for England and Wales [22]. The QALY decrement for IPD is estimated based on the data from the US Centers for Disease Control and Prevention’s Active Bacterial Core Surveillance for 2013. The study also investigates a scenario with higher QALY decrements.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	The IPD incidence and case-fatality rates stratified by the serotype-groups, age-cohorts and health risk groups are obtained the Centers for Disease Control and Prevention’s Active Bacterial Core surveillance in 2013.The incidence rates and case-fatality for inpatient- and outpatient NBP stratified by age-cohorts and health risk groups are obtained from previously published studies conducted for the US. These rates are modified to account for the indirect effects of the pediatric vaccination with PCV13. The changes in the rates are given for the years between 2003 and 2009 across the serotypes groups (“PCV7 types”, “PPSV23 types not in PCV7”, “Types in neither PCV7 nor PPSV23”) and are based on data of the Active Bacterial Core Surveillance for 2013. The vaccine effectiveness estimates for PCV13 are obtained from the CAPITA trial. The vaccine effectiveness estimates for PPSV23 are obtained from two published systematic reviews.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	The applied discount rate complies with the U.S. Panel on Cost-Effectiveness in Health and Medicine [24].
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	The uncertainty of the following parameters are tested in the multivariate SA: • costs (as the 5th and 95th percentiles for a log-normal distribution) • QALY (a uniform distribution between the high and low QALY scenario) • IPD incidence rate • Inpatient NBP rate • Case-fatality rates for NBP • Percentage of NBP due to PCV13 types • Effectiveness parameters for both vaccines • Vaccine coverage Alternative scenarios are evaluated in one-way sensitivity analyses:

			• PCV13 with much more rapid waning: "no waning for 5 years followed by waning to zero over 15 years" • vaccine prices (2 scenarios) • PPSV23 effectiveness of 45 % against vaccine-serotype NBP Additionally: increased herd protection.
11	Conclusion	Are conclusions supported by results?	The conclusion of this study is that the addition of one dose of PCV13 to the vaccination with PPSV23 and replacement of PPSV23 with PCV13 are cost-effective strategies. Herd effects of the pediatric vaccination strongly influence the cost-effectiveness estimate of PCV13.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)			
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** England		**Study:** van Hoek, Albert Jan; Miller, Elizabeth (2016): Cost-Effectiveness of Vaccinating Immunocompetent /=65 Year Olds with the 13-Valent Pneumococcal Conjugate Vaccine in England. In PloS one 11 (2), e0149540. DOI: 10.1371/journal.pone.0149540.	
Completeness and consistency of reporting economic evaluation			
Type of evidence		**Question**	**Rationale** / **Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	This study reports all the dimensions of the economic evaluation to some extent. The reporting can be considered partly transparent. The information is consistent across the sections of the study. The paper has gaps about the structure of the developed model, applied PPSV23 VE, estimation of costs per case and details of the sensitivity analyses. The aggregated costs per case are given. Methods for applying indirect effects are described with provision of the respective incidence rates. **1 ☐ Many gaps/ inconsistent** **2 ☒** **3 ☐** **4 ☐ Complete and consistent**
	Dimension	**Question**	**Comment**
1	Target population	Is the target population for this intervention defined?	The target population is defined as a cohort of immunocompetent individuals ≥65 years old including people in clinical risk-groups.
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: adding PCV13 to the current PPVS23 vaccination practice of individuals aged 65 years and over. Two strategies are considered: • add PCV13 for immunocompetent population • add PCV13 for people in clinical risk-groups Vaccine coverage is 69%. The cost-effectiveness is evaluated using a threshold of £20,000 as is recommended in by the National Institute for Health and Clinical Excellence in the UK.

3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The model is a static cohort cost-effectiveness model. Model start is the autumn of 2016. The model computes future incidence, costs and health outcomes across age groups. The model structure is not reported.
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The analyses are performed in comparison with vaccination with a dose of PPSV23 of individuals aged 65 years and over.
5	Perspective	Are the perspective of analysis and its rationale stated?	The analyses are performed from a health care payer's perspective.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The study reports a cost-effectiveness analysis of adding PCV13 to the current pneumococcal vaccination practice. The cost-effectiveness of the evaluated intervention is expressed in £/ QALY gained and compared with the recommended threshold of £20,000.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* IPD and CAP incidences for vaccine types ("PCV7 and PCV13 minus 7") are reported with the sources. The approach to calculation of the incidence for the non-risk population is reported. Observed and projected incidence is reported. The projections of the indirect effects of the pediatric vaccination with PCV7 and PCV13 are described. *Vaccine-related parameters:* Vaccine effectiveness and duration of the protection for the PCV13 against IPD and CAP are reported. • VE PCV13 against IPD: 75% • VE PCV13 against CAP: 45.6% The following waning rate for PCV13 is reported: • against IPD: constant for 9 years, 43% for year 10-14, 9% for year 15-19, 5% for 20+. • against CAP: constant for 9 years, 26% for year 10-14, 5% for year 15-19, 3% for 20+. We calculated years of full protection and average duration of protection with PCV13 against IPD and CAP: • 12.53 years of full protection against IPD and 12.46 against CAP • average duration of protection is 9.4 years against IPD and 5.7 against CAP. Although the study compares an addition of PCV13 to the current vaccination with PPSV23, PPSV23 VE is not reported. *Costs:* the study reports costs of hospitalization due to IPD (age-dependent range) and CAP and vaccination costs. *Health outcomes:* age dependent values for QALY loss are reported with the source.
8	Time horizon	Is the time horizon reported?	The time horizon is lifetime.
9	Discount rate	Is the discount rate reported?	The discount rates are reported: cost and QALYs: 3.5% annually
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Sensitivity analyses are briefly described.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and	The results are reported for the base-line and sensitivity analyses. The results of the economic evaluation include estimated cases, deaths, total costs, QALYs lost and ICERs.

		effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	The resulted cost-effectiveness ratio is £257,771/QALY gained

Relevance and validity of economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	This study evaluates elderly vaccination with both PCV13 and PPSV23 against IPD and CAP. It uses a relevant population, comparator, costs and outcomes and performs analyses from the relevant perspective. The modeled population is a single cohort. The study does not contain a description of the model design and methods of sensitivity analyses making it hard to evaluate validity and relevance. The study includes the herd effects of the pediatric vaccination with PCV13 projecting the effects of PCV7 on the IPD incidence among adults based epidemiological data from the country. The study applied relevant vaccine effectiveness for PCV13 and a conservative approach to the duration of the vaccine protection.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☒** **4 ☐ High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The studied population is a cohort of immunocompetent people 65 years old and older. The co-morbidities include diabetes, asthma, splenectomy or heart, liver or lung disease. The modelled population is intended to resemble the targeted population of the CAPITA trial.	
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study considers addition of PCV13 to the current vaccination strategy using PPSV23, so that both vaccines are used for the vaccination. Other scenarios such as replacement of PPSV23 with PCV13 are not considered. The program under evaluation includes additional GP visit for administration of PPSV23 which is included in the cost calculation. The vaccination coverage is based on the current vaccination program and is seen as valid.	
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The study does not provide a description of the model structure making it difficult evaluate the modeled event pathway.	
4	Comparator	Does the choice of comparators reflect current practice?	The comparator is the current vaccination practice. No-vaccination comparator is not considered.	
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The perspective is a health care payer's in accordance with the "Guide to the methods of technology appraisal" by NICE[25]. A personal social services perspective is not considered. The relevant aggregated hospitalization costs for IPD and CAP are obtained from a previously published economic analysis of vaccinating risk groups with PCV13 in England [26]. The vaccine price is given by the British National Formulary. All costs are given in British pounds of 2014.	
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate	The selected health outcomes, QALY, are in accordance with the requirements of NICE. The values for QALY loss are obtained from a previously published cost-effectiveness study for England[26].	

		PRO valid? Are assumptions for outcomes selection valid?	
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	IPD incidence by the vaccine-type is obtained from "the serotype-specific surveillance data collated by Public Health England" (July to June, 2002/03 -2013/2014). CAP incidence by the vaccine-type is obtained from a longitudinal survey conducted in "two large teaching hospitals in Nottingham (UK)". The values for case-fatality rates, life expectancy and costs are obtained from national sources. Herd effects of the pediatric vaccination with PCV13 are applied as a projection of PCV7 effects based on the assumptions that circulation of PCV7 serotypes reached a post-vaccination steady state in IPD (made based on epidemiological data) and that the CAP incidence experience the same trends as IPD. Vaccine effectiveness for PCV13 is obtained from the CAPITA trial. The duration of protection is applied based on recommendation from Pfizer stated in its report: " Cost-effectiveness analysis of adult vaccination with the 13-valent Pneumococcal Conjugate Vaccine in the United Kingdom, unpublished report provided to the authors by Pfizer" Vaccine effectiveness for PPSV23 is not stated. Vaccine coverage is applied based on the current vaccination practice.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	The applied discount rate is recommended by the "Guide to the methods of technology appraisal" by NICE[25].
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	The effects of the following parameters are tested in the sensitivity analyses: • Double hospital costs • 0.05 QALY loss both IPD CAP • 15%/ 5% CFR IPD/CAP • 30%/ 15% CFR IPD/CAP • Variation of age at vaccination 70, 75, 80 • No waning • No back ground QALY loss • Extra long life expectancy • Double the CAP incidence • Long term equilibrium (2018) • Incidence 55%, to reflect no risk Additionally relation between the cost-effectiveness ratio and vaccine is evaluated in the sensitivity analysis to determine the vaccine price "at which the vaccine becomes cost-effective using a threshold of £20,000 as is recommended in the UK".
11	Conclusion	Are conclusions supported by results?	The study concludes that usage of both PCV13 and PPSV23 for vaccinating the immunocompetent elderly can be efficacious but is unlikely to be cost-effective with given threshold of £20,000. The optimal age of vaccination is suggested 75 years "due to the waning protection and the increase in incidence with age". The study points out that the effects of the pediatric vaccination with PCV13 on the incidence among the elderly make the elderly vaccination with PCV13 not cost-effective.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal conjugate vaccine (PCV13) **Setting:** Australia			**Study:** Dirmesropian, S.; Wood, J. G.; MacIntyre, C. R.; Beutels, P.; McIntyre, P.; Menzies, R. et al. (2017): Cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) in older Australians. In Vaccine 35 (34), pp. 4307–4314. DOI: 10.1016/j.vaccine.2017.06.085.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	The model is very detailed as many parameters are age-stratified and almost all parameter values are reported. However, some information is not stated (e.g., vaccination rates) or it is ambiguous which values are used in the base case (e.g. PCV13 vaccine efficacy). All estimates are based on data or published literature and the information is consistent across the different parts of the paper. Some information on the resource use is missing or the costing is simplified.	**1 ☐ Many gaps/ inconsistent** **2 ☐** **3 ☒** **4 ☐ Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The modeled population is defined as a single-cohort of the general population, stratified by age groups 65-69, 70-74, 75-79, 80-84 and ≥85 years. No risk groups or risk factors are considered by the model.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	The intervention is the vaccination of 65-year-old persons with PCV13 or PPSV23 at the start of the model. Other ages of the vaccination start are explored in the model. Vaccination for PPSV23 uptake is: 65-67 years: 33.4% ; 68-69 years: 44.5% ; 70-74 years: 55.2% ; 75-79 years: 67.6% ; 80-84 years: 62.9% ≥85 years: 61.9% Additionally, the administration of PPSV23 5 years after PCV13 is explored. The uptake for PCV13 is not stated in the methods section, but the results section indicates, that a 60% vaccine uptake is assumed for PCV13.	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The study applies a single cohort Markov model with a cycle length of one year, following 65 year old persons up until the age of 100. No illustration of the model layout is shown. The health states/disease categories are hospitalizations and death due to IPD as well as GP consultations, hospitalizations and deaths from non-invasive CAP. A detailed outline of the related calculations is given in the appendix. IPD cases are further stratified into meningitis, bacteremia and (invasive) pneumonia. It is unclear if the states are mutually exclusive, e.g. if a patient may be hospitalized after a GP visit. Probabilities are given for GP consultations, hospitalizations, deaths and IPD manifestations. Detailed, age-stratified data on costs is given in the appendix.	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	PCV13 is compared to the current practice of PPSV23 vaccination, assuming the same uptake for both strategies. In the base case both strategies are applied to 65-year-old persons and compared against each other and against a “no vaccination” scenario.	
5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis is conducted from a healthcare system perspective. No recommendation for the perspective is cited. No other perspective is explored in the sensitivity analyses.	
6	Type of	Is the type of analysis stated? Is the rationale for	Cost-effectiveness analysis of PCV13 vaccination for the elderly (65 years) compared to the current PPSV23 strategy. The main	

	analysis	outcomes selection (effectiveness measure or utilities) stated?	outcome of the study is incremental costs per QALY gained (ICER). The outcomes of the analyses are total costs stratified into program costs and healthcare costs and QALYs. Avoided hospitalizations and deaths are reported for IPD and CAP and additionally GP consultations for CAP.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	Age-specific (65-69, 70-74, 75-79, 80-84, ≥85) input parameters are given on the number GP visits for CAP, the respective probabilities of hospitalizations and death for meningitis, bacteremia, pneumonia and CAP. Also, the age-specific proportion of CAP due to pneumococci and the respective proportions of IPD due to PCV13 and PPSV23 are given. Sources are given for all these parameters. Following national data, the incidence rates of the vaccine-preventable serotypes is assumed to be stable. *Vaccination related parameters:* *Efficacy:* PCV13 IPD: 89.2% for 65-year-old. Adapted from Van Werkhoven et al. Fitted logistic regression for age-specific values, but only examples are given (89.2% for 65 years, 77.1% at age 75). All values are given as a plot of the logistic curve. CAP: 60.4% for 65-year old. Same as for IPD with example values being 60.4% at 65 years and 35.5% at 75 years. PPSV23 IPD: Fitted logistic regression resulting in age-specific VE of 0.58/(1+2.2898^age-85.5). Data used for fitting is 58% for 65-74-year old, 56% for 75-84-year old and 48% for ≥85-year old, calculated from the 12% VE for this age group in Andrews et al. and the 58% and 56% of the previous age groups. CAP: none *Waning:* Vaccine efficacy for PCV13 was assumed to stay constant for the first 5 years following the CAPITA study, followed by a linear decline to zero for the next 5 years. For PPSV23 a 2-year period of constant efficacy was assumed followed by a 3-year linear decline. *Years in full protection:* PCV13: IPD 7.50, CAP 7.50 PPSV23: IPD 3.73, CAP n.a. Vaccination costs were A$65 for PCV13 and A$35 for PPSV23 with A$10 for administration costs for both vaccinations. Costs for a GP visit are priced at A$114 and detailed hospitalization costs are given in the appendix. Sources and calculations are also given in the appendix. QALY loss was 0.0709 for IPD and CAP inpatients and 0.0045 for CAP outpatient patients. Another model is cited for the utility values. Population norms are used.
8	Time horizon	Is the time horizon reported?	The cohort 65-year old persons is followed until death or up to 100 years of age. This corresponds to a 35-year time horizon.
9	Discount rate	Is the discount rate reported?	Costs and outcomes are discounted at 5% annually, as recommended by national guidelines.
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Sensitivity analyses include univariate, multivariate (scenario) and probabilistic analyses. Results from the latter are reported as CEACs. A complete list of the parameters varied in the SA are given in the appendix along with the parameter distributions used for the probabilistic analysis. SA for different sources of input parameters are explored. The most influential parameters are • Proportion of CAP due to PCV13 serotypes

			• PCV13 vaccine price • Duration of protection • VE for the vaccine-type pneumococcal CAP • Proportion of CAP due to *S. pneumoniae*
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	Disaggregated results are reported for the cost components as program costs and healthcare costs as well as for total QALYs lost. Further information is given about the avoided hospitalizations, deaths and GP consultations. ICER vs no vaccination: PCV13 = A$ 88,000/QALY and PCV13+PPSV23 A$ 297,200/QALY

Relevance and validity of economic evaluation

Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The research question is relevant as this seems to be the first study to examine the cost-effectiveness of PCV13 compared to PPSV23 in Australia. It is not stated if disease states are mutually exclusive and if there is a treatment pathway used for the costing. Indirect effects through childhood immunization are not incorporated and the model only uses a single cohort.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☒** **4 ☐ High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The study considers five age groups of a single cohort without consideration of risk groups or risk factors. The demographic distribution follows data from the national statistical office (Australian Bureau of Statistics) between 2014 and 2016. The age of the studied population is comparable to the study population of CAPITA by age and it does correspond to the population mainly targeted with the new vaccination strategy.	
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study compares the current vaccination scheme with PPSV23 in 65-year old persons with a PCV13 vaccination strategy for the same age. Additionally, different ages of the vaccination are explored. The study evaluates the effectiveness of the different strategies against IPD-related mortality and hospitalizations as well as CAP-related mortality, hospitalizations and GP visits. Vaccine coverage is based on currently observed uptake data for PPSV23. For PCV13 a 60% uptake was assumed.	
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The following events are included in the model: IPD and CAP hospitalization, IPD and CAP death, CAP GP visit. All IPD events are further stratified into meningitis, bacteremia and pneumonia. It is not clear how mutually exclusive the different health states are, e.g. if a patient that is hospitalized for CAP can also have GP visits. Transition to the disease state is influenced/prohibited for vaccinated persons under consideration of vaccine effectiveness.	
4	Comparator	Does the choice of comparators reflect current practice?	The authors state that PCV13 has already been recommended for older adults. It seems that no previous study has been conducted to evaluate the cost-effectiveness of this decision to replace PPSV23 by PCV13 in older adults.	
5	Perspective	Is the perspective chosen valid? Are all relevant costs	The analysis is conducted from the healthcare payer perspective and no other perspective is evaluated in the sensitivity analyses.	

	and costs	considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	Direct health care costs consist of inpatient costs, GP visits and vaccine and administration costs. All cost data are based on published data and are listed in the appendix. The costs are aggregated per health state making it hard to assess the details of the price-resources framework, e.g. we did not find the number of GP visits associated with the different health states. All costs are adjusted to the reference year of 2016.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	National, age-specific population norms are used to calculate the QALY losses. Utility weights for IPD and CAP hospitalization and for a CAP-related GP consultation are taken from the literature, i.e., a previously published model from a different country (Netherlands). The QALY losses associated with hospitalization contain the period of the acute illness and 1 month follow up.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	Incidence, by age group: IPD hospitalization incidence is derived from Australian data collected by the National Notifiable Disease Surveillance System (NNDSS) CAP hospitalization incidence is taken from the National Hospital Morbidity Database (NHMD), all-cause CAP was used to extract data from this database, the proportion of *S. pneumoniae*-related CAP is taken from Charles et al. (2008) IPD mortality is also based on NNDSS data. CAP mortality has been taken from the study by Kothe et al. (2008)[27] CAP GP consultations were taken from a previous, Australian model (Newall et al. 2011). Indirect effects through herd immunity induced by the childhood vaccination are incorporated in the model. Age-specific vaccine efficacy of PCV13 is taken from the CAPITA study [28]. PPSV23 age-specific, vaccine efficacy is taken from Andrews et al. (2012) [13]. Waning has been based on evidence from the literature.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	The time horizon is 35 years to follow all persons initially vaccinated at the age of 65 to be followed until their death of the age of 100.
9	Discount rate	Is the recommended discount rate applied?	The discount rate for costs and outcomes is 5% annually, but no guideline for the discount rate is cited. However, the discount rate corresponds to the recommended rate.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	Six different scenarios are explored in the sensitivity analyses as described in the appendix. The following are reported to be most influential: • Proportion of CAP due to PCV13 serotypes • PCV13 vaccine price • Duration of protection • VE for the vaccine-type pneumococcal CAP • Proportion of CAP due to *S. pneumoniae* One additional analysis was performed on the vaccine price of PCV13. Distributions for the parameters are given in the appendix.
11	Conclusion	Are conclusions supported by results?	The results indicate that both PCV13 and PPSV23 are not cost-effective compared to a no-vaccination strategy (A$ 88,000/QALY and A$297,200/QALY, respectively), but that PCV13 is cost-effective when compared against the current

			practice of PPSV23 (A$35,300/QALY).

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** Korea			**Study:** Heo, Jung Yeon; Seo, Yu Bin; Choi, Won Suk; Lee, Jacob; Noh, Ji Yun; Jeong, Hye Won et al. (2017): Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. In PloS one 12 (5), e0177342. DOI: 10.1371/journal.pone.0177342.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	The study reports all of the main input parameter values in great detail but is less precise on the perspective and the time horizon of the model. Results are not presented in great detail.	**1** ☐ **Many gaps/ inconsistent** **2** ☐ **3** ☒ **4** ☐ **Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The target population is the general population above 65 years. The model population is stratified into the age groups 19-49, 50-64, 65-74 and ≥75 years. There is a further stratification into low, moderate and high-risk groups taken from a previous study. High risk: (1) splenic dysfunction including post-splenectomy status, (2) hematologic malignancy such as multiple myeloma, leukemia, or lymphoma, (3) a condition affecting the bone marrow or lymphatic system, such as chemotherapy with alkylating drugs or antimetabolites, or radiation within the previous three months, (4) solid organ or stem cell transplantation, (5) chronic renal disease such as nephrotic syndrome or chronic renal failure, (6) HIV infection, (7) high-dose corticosteroid use (≥ 20 mg/day of prednisone or an equivalent) lasting two or more weeks, or (8) treatment with a recombinant human immunomodulator. Moderate risk: (1) diabetes mellitus, (2) chronic liver disease, (3) chronic pulmonary disease, such as asthma or chronic obstructive lung disease, or (4) chronic cardiovascular disease, such as heart failure, cardiomyopathy, or other chronic conditions affecting cardiac function. Low risk: None of the above.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	The model evaluates the effectiveness of a PCV13 and/or PPSV23 vaccination scheme for persons ≥65 years compared to the current practice of PPSV23 alone. It is unclear whether the vaccine administration happens at the model start, but it is stated that the age group 65-74 is vaccinated in the base case. *Vaccine uptake:* Vaccine uptake for persons 65 years and older is assumed to be either 60% or 80% assuming the same	

			vaccinations rates as for PPSV23 and influenza, respectively.
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The study applies a Markov model which is illustrated in figure 1. It is unclear whether it is a multi-cohort model, but as no information is given about the re-entering of new cohorts, it may thus be assumed to be a single-cohort model. Patients from each risk group can develop IPD or NPP, each leading to disability or death. Costs and PROs as measured by QALY loss are attributed to the health states IPD and NPP. No costs and QALY losses are given for the "Disabled" disease state. Transition probabilities are given as independent proportions and incidence rates.
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The current status quo – PPSV23 only – in adults 65 years and older is compared to PCV13 alone and PCV13 and PPSV23 combined for the same age group. This is also tested for vaccination of the age group 50-64 years. The rationale is the necessity to update the national immunization program.
5	Perspective	Are the perspective of analysis and its rationale stated?	The perspective is not directly described. However, the authors state that cost-effectiveness is assessed in a "societal context" and report indirect costs, which allows for the conclusion that the analysis is conducted from a societal perspective.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The analysis estimates the cost-effectiveness of a vaccination with PCV13 and/or PPSV23 in the elderly (65 to 74 years) compared to the current strategy of PPSV23 alone in the same age group. Results are mainly given as ICERs (Costs per QALY). Single estimates for costs, incremental costs, QALYs and incremental QALYs are given as well.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* The age-specific incidence rates for IPD and NPP are taken from a previous study examining data between 2011 and 2014. Risk ratios from a national database for CAP are used to adjust for risk group specific incidence rates. IPD age and risk group specific fatality rates are taken from a national, multi-center study and NPP fatality rate have been taken from the same study as the incidence rates. Sources are given for all parameters. The case-fatality rate is modified ex-post through expert opinions elicited via a Delphi panel. *Vaccination related parameters:* *Efficacy:* PCV13 IPD: 79.4% (< 65 years), 75.0% (65-74 years), 62.8% (≥75 years) CAP: 52.0 (< 65 years), 45.0% (65-74 years), 37.7% (≥75 years) PPSV23 IPD: 95.3% (< 65 years), 82.0% (65-74 years), 68.7% (≥75 years) CAP: none Vaccine efficacy is modified ex-post through expert opinions elicited via a Delphi panel, i.e. PPSV23 VE against IPD was lowered by 20% and to 20% for moderate and high-risk patients, respectively, and 15% and 22% lower for PCV13. For NPP PCV13 VE is 20% and 35% lowered for moderate and high-risk patients. *Waning:* Estimates on waning are taken from Smith et al. 2012 [29]. For PCV13 VE is still 39.7/29.1/0 percent against IPD and 25.9/17.5/0 for the age groups <65/65-74/≥75 years after 15 years. *Years in full protection:* PCV13: IPD 9.83/9.65/4.23 years in the <65/65-74/≥75 years age groups CAP 9.78/9.66/4.22 years PPSV23: IPD 6.68/5.10/3.84 years CAP: none Vaccination costs are $50.31 for PCV13 and $14.13 for PPSV23 with $15 for administration costs for both vaccinations. Direct medical costs are age- and risk group specific, based on a previous study and varied between $5,404 and 8,609 for IPD and

			$1,055 and $2,986 for NPP. Sources are given. QALY loss is calculated using the age- and risk-group stratified length of stay and the Korean population norms. The utility-values are taken from another modeling study (Smith et al. 2012) [29], which took the values from another modeling study.
8	Time horizon	Is the time horizon reported?	The time horizon is 15 years, but it is stated that costs and outcomes if survivors of this time frame are considered using their further life-expectancy. It can therefore be assumed that the time horizon is life-long. No sensitivity analysis was performed on the time horizon.
9	Discount rate	Is the discount rate reported?	Costs and benefits are discounted at 5% per annum as recommended by national guidelines. No sensitivity analysis is conducted on the discount rate.
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Deterministic sensitivity analysis is performed by setting parameters values to 25% for the lower bound and 125% for the upper bound. Additionally, PPSV23 efficacy against NPP is varied between 20% and 50% in the sensitivity analysis (0% in the base case). Results are presented for: Vaccine Effectiveness: PCV13 NPP &IPD, PPSV23 IPD Disease incidence: NPP & IPD Costs: Medical costs NPP & IPD, Vaccine price PCV13 & PPSV23, Other direct costs NPP & IPD, Productivity loss NPP & IPD Mortality: NPP & IPD case fatality, general mortality Utility: Population norms, NPP & IPD utility values Probabilistic sensitivity analysis was performed with 1,000 draws from triangular distributions.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	Costs and QALYs are reported disaggregated, but not further stratification of results is provided. Results are reported for the base case and the sensitivity analyses. PCV13 alone compared to the current strategy of PPSV23 alone showed an ICER of $797/QALY for 60% vaccination rate and $701/QALY for 80% vaccination rate. This strategy is also cost-effective for each of the risk and age groups.

Relevance and validity of economic evaluation

Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The graphical representation of the model is somewhat ambiguous and the range for parameter values in the deterministic sensitivity analysis are very unusual. Indirect cost calculations seem to be missing for some disease states or manifestations of IPD.	**1 ☐ Low relevance/ validity** **2 ☒** **3 ☐** **4 ☐ High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness	The target population is relevant. The model population consists of persons of 65 years and older and is stratified by age and different risk groups. It is comparable to the study population of VE regarding the age of the study population. Age group distribution has been taken from national statistics and distribution across risk groups has been taken from a national study. The	

		data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	division into risk groups is based on co-morbidities, but prevalence estimates of those diseases are not explicitly listed.
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates single-dose PCV13 vaccination and sequential PCV13/PPSV23 vaccination compared to a single-dose PPSV23 vaccination against NPP and IPD. No further stratification is made into outpatient and inpatient CAP or IPD. The vaccination strategies are only evaluated for the age group of 65 to 74 years of age.Coverage rates are based on observed PPSV23 and influenza vaccination rates and are not differentiated by risk group. One-time vaccination.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The graphical representation of the model lists the health states “NPP”, “IPD”, “disabled” and “death” and it does not differentiate between inpatient and outpatient treatment. It is unclear, what constitutes the health state “disabled”, i.e. no list of sequelae is given, no costs or QALY losses are given for this health state. After suffering IPD or NPP, patients may return to their “healthy” state or progress to “disabled” or “death”. Transition to these states is influenced by vaccination coverage, vaccine effectiveness and the age- and risk-group. Indirect effects from childhood vaccination are also incorporated, assuming a similar decrease of the PCV13 serotypes as being observed after the introduction of PCV7.
4	Comparator	Does the choice of comparators reflect current practice?	The PCV13 vaccination as a single dose or a combination with PPSV23 is compared to the current practice of PPSV23 alone for persons ≥65 years old.
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The authors only state to conduct the analysis in a “societal context”, which can be interpreted as a societal perspective. No guidelines are cited, making it difficult to judge the validity of the perspective in the Korean context. Costs for IPD and NPP are listed in an aggregated form and they are taken from a previous national study on direct health care costs. Indirect cost seems only to be calculated for the productivity loss of the patient for the length of stay. It is unclear whether forgone productivity loss due to pre-mature mortality is included or if the Human Capital or the Friction Cost approach have been used. Costs for the “disabled” state are not given. The reference year is not clearly stated.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	QALYs are given as the only and primary outcome measure. Utility estimates are based on national population norms and are multiplied with the utility weights from the study of Smith et al. QALY loss is only calculated for IPD and NPD. No utility decrement is listed for the “disabled” health state.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	Serotype distribution is taken from national surveillance data. Age-specific incidence rates for IPD and NPP are based on data from a national catchment area. Risk-group specific incidence rates are calculated based on the assumption that the risk ratio of CAP versus the general population is transferable to IPD and NPP. Case fatality rates for IPD are age- and risk group specific and taken from a national multi-center study. NPP case fatality rates are based on a multi-center catchment area study. Inconsistent values have been resolved via Delphi panel. No figures or sources of background mortality are given. Indirect effects are calculated from the observed effects after the introduction of PCV7. The trajectory of an American study by Moore et al. (2015) [30] are applied to the national data. Based on the Delphi panel, indirect effects on NPP are assumed to be 50% of the IPD effects. Using non-serotype specific data is not a valid method and biases the analysis towards PCV13. Methods for the extrapolation of Moore data are not described. Age-specific vaccine efficacy data is taken from the CAPITA study for PCV13 and PPSV23 from a Cochrane Review [31].

			PPSV23 VE is age-adjusted according to Smith et al. 2012 [29]. Other parameters (costs, QALYs) are mainly from national sources.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	The time horizon is set to 15 years in the base case and no sensitivity analyses are performed on the time horizon. As the age group being vaccinated spans 20 years and vaccine efficacy is longer than 15 years, a longer time horizon may lead to different results.
9	Discount rate	Is the recommended discount rate applied?	Costs and outcomes are discounted at 3%, but no guideline is cited. No sensitivity analysis is performed on the discount rate.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	The values in the deterministic sensitivity analysis are set to 25% and 125% of the base case value. Vaccine effectiveness, costs and QALYs are varied in the analyses, but time horizon or discount rate are not explored. The ranges are set to rather unusual values and the corresponding tornado plot looks skewed.
11	Conclusion	Are conclusions supported by results?	Based on the results the study concludes that PCV13 alone or in combination with PPSV23 is more cost-effective than PPSV23 alone. All scenarios are only compared to a "no vaccination" scenario and no ICER is reported comparing the different strategies.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal conjugate vaccine (PCV13) **Setting:** Australia			**Study:** Chen, C.; Wood, J. G.; Beutels, P.; Menzies, R.; MacIntyre, C. R.; Dirmesropian, S. et al. (2018): The role of timeliness in the cost-effectiveness of older adult vaccination: A case study of pneumococcal conjugate vaccine in Australia. In Vaccine 36 (10), pp. 1265–1271. DOI: 10.1016/j.vaccine.2018.01.052.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	The study reports most parts of the study in great detail, but the paper represents an adaption of a previous paper and is used to analyze the effect of the age at vaccination on the cost-effectiveness.	**1** ☐ **Many gaps/ inconsistent** **2** ☐ **3** ☒ **4** ☐ **Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target	Is the target population for this intervention defined?	The model considers a multi-cohort population representative for the general population between 65 and 100 years with an one-	

	population		year age stratification. Persons above 100 years are aggregated into one age group. There is no consideration of risk groups or risk factors.
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	The study aims to compare a no vaccination scenario with the current uptake pattern of PCV13 vs. a scenario where vaccination takes place exactly at the age of recommendation for all eligible persons, respectively. *Vaccine uptake:* The vaccine uptake from the status quo is presented in a graphical form for every year of age with a peak of 66 of roughly 7% and an exponential decay over the following years of age. Average age is 70.5 years with 54.9% of persons being vaccinated over the age of 70 years. In the alternative scenario 54.9% were vaccinated at the age of 65. The study also explored the optimal age for both alternative scenarios (observed vs. recommended age).
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The model has been adapted from a previously published CEA analysis. There is no graphical representation of the model. The cycle length is one year. The model attributes costs and QALYs to the events "inpatient IPD" stratified into meningitis and non-meningitis IPD, "outpatient CAP", "inpatient CAP".
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The current vaccination strategy is compared with a hypothetical uptake of the vaccine "at once" at the recommended age. The rationale for the analysis is given, as recommendations for the age of vaccination should consider that not every eligible person is vaccinated exactly at that age.
5	Perspective	Are the perspective of analysis and its rationale stated?	The evaluation is conducted from a health care payer perspective as recommended by the national guidelines. No sensitivity analysis is performed on the perspective.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The cost-effectiveness of "no vaccination" vs. the recommended vaccination age or the observed vaccination age is calculated as costs per QALY (ICER). Other outcomes include the number of GP visits as well as the number of deaths (prevented) and the number of hospitalizations due to meningitis, bacteremia, IPD pneumonia and CAP, respectively. The administered doses, program costs, health care costs and QALY gains are also listed separately.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* IPD incidence and fatality rates are stratified by 5-year age groups, CAP incidence, fatality and hospitalization rates are not stated to be age-specific. It was assumed that vaccine-type incidence of CAP was equal to IPD incidence. IPD incidence is also inflated to a "no vaccination" scenario which unfortunately not described in the appendix. Indirect effects of PPSV23 are not included as there is no evidence supporting this assumption, but indirect effects for PCV13 childhood vaccination are considered. *Vaccination related parameters:* *Efficacy:* PCV13 IPD: Maximum(1 – 0.118 x 1.078^(age-65),0) CAP: Maximum(1 – 0.396 x 1.050^(age-65),0) PPSV23 IPD: 0.58 (50-74 yoa), 0.56 (75-84 yoa), 0 (>85 <yoa) CAP: none *Waning:* PCV13 It is assumed that waning sets in after 5 years and that the efficacy thereafter declines linearly to zero over the next 6 years PPSV23 It is assumed that waning sets in after 2 years and that the efficacy thereafter declines linearly to zero over the next 3

			years *Years in full protection:* PCV13 IPD 7.50 years CAP 7.50 years Vaccination costs were $AUD 65, costs for a GP visit were $AUD 126. Hospitalization costs are based on a previous study. QALY loss was 0.0709 for IPD and CAP inpatients and 0.0045 for CAP outpatient patients. Another model is cited for the utility values. Population norms are used.
8	Time horizon	Is the time horizon reported?	It can be assumed that the time horizon of the model is 10 years, which marks the end of the program. The sentence "with each cohort being followed until vaccine-induced immunity has fully waned and the full consequences of any death included" also allows to interpretation for a life-long time horizon. The reference year for costs is 2016.
9	Discount rate	Is the discount rate reported?	Costs and outcomes are discounted at 5.0%, respectively, as recommended by national guidelines.
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	No sensitivity analyses are conducted. The justification is that authors did not want to focus on uncertainty.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	Results are reported for prevented deaths, program costs and health care savings as well as QALYs and cost-effectiveness. The cost-effectiveness estimate is $AUD83,538/QALY for the recommended age of vaccination and $AUD65,269/QALY for the observed uptake approach, each compared against no vaccination. The ideal age for the recommended scenario is 75 years and 72 years in the observed scenario.

Relevance and validity of economic evaluation

Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The study question is not a classical cost-effectiveness analysis, but on the timeliness of PCV13 vaccination, i.e. what the optimal age for the vaccination. Nearly all parameters of the model are given, although the costing for the different health states seems to have a very simple treatment pathway. No sensitivity analyses have been conducted which is justified by the focus of the study.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☒** **4 ☐ High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The study considers a population above 65 years and has a one-year age stratification. The stratification and the demographic process follow the numbers from the national bureau of statistics. IPD incidence is calculated for 5-year age bands from data of the National Notifiable Diseases Surveillance System. The population is split into single years of age and corresponds to the age groups used in the CAPITA study.	

2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates adult pneumococcal vaccination against IPD, inpatient and outpatient CAP. The primary aim of the study compares an "all at once" vaccination strategy at the recommended age vs. the current vaccination accumulating over the years. The latter strategy uses real world data from a New South Wales (NSW) survey. The secondary aim of the study examines the ideal age for the "at once" and the cumulative vaccination strategy.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	IPD (as meningitis and bacteremia, respectively), inpatient and outpatient CAP are modelled. All probabilities are taken from national data or sources.
4	Comparator	Does the choice of comparators reflect current practice?	The comparator is the actual current practice, i.e. vaccine uptake for PCV13 for persons over 65 years builds up cumulative, instead of all persons vaccinated at once, with the average age of vaccination at 70.5 years.
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The perspective of the healthcare payer is recommended by national guidelines. No other perspective is taken in the sensitivity analyses. The costing is described in the appendix and it seems that all relevant aspects have been considered (vaccine costs, administration costs, inpatient costs for IPD and CAP and outpatient costs for CAP). However, no treatment pathway is described and it seems as IPD patients are only treated in hospitals. Inpatient costs have been collected by age.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	QALYs are given as the primary outcome measure. QALY losses have been taken from a Dutch study and have been combined with Australian population norms. QALY loss is differentiated between IPD inpatient, CAP inpatient and CAP outpatient. No information is given on the duration and the utilities used to arrive at the QALY values. Decrements for deaths are also included in the calculations.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	IPD incidence, serotype distribution and case fatality is calculated from national registry data and all sources and calculation procedures are described in the appendix. CAP prevalence is based on the assumption that pneumococcal diseases cause 13.9% of all CAPs and that the proportion of CAP attributable to the PCV13 serotypes was the same as for IPD. CAP fatality rates are not reported. Indirect effects for childhood vaccination are incorporated. The appendix states that due to the stabilized incidence of the PCV13 serotypes between 2011 and 2015, future serotype distribution would be the same as in 2015.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	The duration of the vaccination program in the model is 10 years and the model states that all consequences have been included in the results, which would correspond to a life-long perspective.
9	Discount rate	Is the recommended discount rate applied?	The discount rate of 5% for costs and outcomes has been applied following national guidelines.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	No sensitivity analyses have been conducted.
11	Conclusion	Are conclusions supported by results?	Based on the results the authors conclude that the timeliness of vaccination plays an important role and should be considered for vaccination recommendations.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal conjugate vaccine (PCV13) **Setting:** Australia			**Study:** Chen, C.; Beutels, P.; Newall, A. T. (2018): Evolution over time in the cost-effectiveness of pneumococcal conjugate vaccine (PCV13) in older Australians due to herd protection from infant vaccination. In Vaccine 36 (16), pp. 2057–2060. DOI: 10.1016/j.vaccine.2018.03.006.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	The paper reports the results of an additional analysis conducted with the model from a previously published study.	**1 ☐ Many gaps/ inconsistent** **2 ☐** **3 ☒** **4 ☐ Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The target population are persons 65 years and older, which are modelled as a multi-cohort Markov model. The model population represents the general population of that age group. The population is stratified into single years of age. No further stratification into risk groups or risk factors is considered.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	The model aims to investigate the influence of serotype evolution on cost-effectiveness estimates for PCV13 in the elderly. Therefore, there is no clear intervention. The two scenarios include one (base case) scenario "[…] of no future serotype changes, only exploring how the past variation in serotypes would have impacted on cost-effectiveness" and one where "[…] 6 additional types in PCV13 were assumed to continue to decline from 2016 in the same way that PCV7 types declined […]". While the alternative scenario is relatively clear, it is not clearly stated how the base case scenario is modelled. Also, the results suggest, that both strategies have been compared to a "no vaccination" scenario. *Vaccine uptake:* The numbers of vaccine uptake are not given directly, but referenced to a previous study of the authors.	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The model has been adapted from a previous study and no model diagram is given. The cycle length is one year. Cost attributions to health states are not stated but referenced to the original model (in this source, costs are attributed to IPD, inpatient and outpatient CAP).	
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	YES. The comparator is described as a scenario where the 6 additional serotypes of PCV13 (vs. PCV7) continue to decline in the same way that PCV7 declined after the introduction of the PCV7 vaccination. The rationale is to explore the uncertainty of the future serotype evolution.	

5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis is conducted from a healthcare system perspective as recommended by national guidelines. No other perspective is considered in the sensitivity analyses.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The study performs a cost-effectiveness analysis of an PCV13 vaccination of the elderly, comparing two different scenarios of the future serotype evolution, probably against a "no vaccination" scenario. The cost-effectiveness (Costs per QALY) of the scenario assuming no change in adult serotypes is lower, than in the scenario with serotype changes. No other outcome measures are stated.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	Most parameters are not directly reported in this study, but in the first publication of the model (see study below).
8	Time horizon	Is the time horizon reported?	The paper states that the vaccination program is evaluated between the hypothetical start in 2012 and the end in 2021, but it is unclear over which period costs and outcomes are documented. This is also somewhat unclear in the first publication of the model, where a life-time time horizon can be assumed for the economic evaluation.
9	Discount rate	Is the discount rate reported?	Costs and outcomes are discounted at 5% as recommended by national guidelines. No sensitivity analysis has been performed on the discount rate.
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	No sensitivity analyses are conducted and no rationale is given for their omission.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	Disaggregated results are reported for program costs, healthcare cost savings, incremental (total) costs, QALY gains and the ICER (Costs/QALY). The ICER for the base case scenario (2016 serotypes) is $AU 71,000 and for the modelled serotype evolution $AUD 171,000. Program costs are identical with $AU 5,690,000 and healthcare savings are $AU 1,164,000 for the base case and $AU 521,000 in the alternative scenario.

Relevance and validity of economic evaluation

Type of evidence	Question	Rationale	Score
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The study can be seen as a sensitivity analysis to a previously published model, looking at the impact of the assumptions about the serotype evolution after the introduction of a new vaccination on the cost-effectiveness estimate. The question is relevant and the design appropriate to answer this question.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☐** **4 ☒ High relevance/validity**

	Dimension	Question	Comment	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The study considers the population of persons 65 years and older. The model uses data from the national statistical office as stated in the cited, predecessor model. The age stratification is in one year bands. From the previous model: IPD incidence is calculated for 5-year age bands from data of the National Notifiable Diseases Surveillance System. The population is split into single years of age and corresponds to the age groups used in the CAPITA study.	
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study aims at the comparison of different assumptions about the serotype evolution after the introduction of a vaccination. It evaluates the impact of a possible decline of the six additional serotypes covered by PCV13 vs. PCV7 to decline in the same way the serotypes of PCV7 have declined after PCV7 introduction on cost-effectiveness compared to the current "stable" incidence scenario. IPD and inpatient and outpatient CAP are included in the analysis. Uptake data is implemented age-specific and taken from a survey.	
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	IPD, inpatient and outpatient CAP as well as death are included in the model. The probabilities for these events are modelled independently via the incidence rates of the respective events. Most details are outlined in the appendix of the original model.	
4	Comparator	Does the choice of comparators reflect current practice?	The base case reflects the current status quo. The comparator explores an equally valid assumption about the serotype evolution. In both scenarios PPSV23 childhood vaccination is incorporated via an indirect effect. No indirect effect of the adult PCV13 vaccination is incorporated.	
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The perspective of the healthcare payer is recommended by national guidelines. No other perspective is taken in the sensitivity analyses. The costing is described in the appendix of the original model and it seems that all relevant aspects have been considered (vaccine costs, administration costs, inpatient costs for IPD and CAP and outpatient costs for CAP). Inpatient costs have been collected by age.	
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	QALYs are given as the primary outcome measure. QALY losses are taken from a Dutch study and have been combined with Australian population norms. QALY loss is differentiated between IPD inpatient, CAP inpatient and CAP outpatient. No information is given on the duration and the utilities used to arrive at the QALY values. Decrements for deaths are also included in the calculations.	
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	IPD incidence, serotype distribution and case fatality are calculated from national registry data. CAP prevalence is based on the assumption of pneumococcal diseases causing 13.9% of all CAPs and that the proportion of CAP attributable to the PCV13 serotypes was the same as for IPD. CAP fatality rates are not reported. Indirect effects for childhood vaccination are incorporated.	
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	The time horizon of the model is 10 years and the model states that all consequences are included in the results. A 5-year duration has been explored in a sensitivity analysis.	
9	Discount	Is the recommended discount rate applied?	The discount rate of 5% for costs and outcomes has been applied following national guidelines.	

	rate		
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	No sensitivity analyses are conducted, besides a five-year time period for the vaccination program.
11	Conclusion	Are conclusions supported by results?	Based on the results the authors conclude that the assumptions on the herd protection from infant PCV13 programs is "critical when assessing the cost-effectiveness of adult PCV13 vaccination in Australia".

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** Netherlands			**Study:** Thorrington, Dominic; van Rossum, Leo; Knol, Mirjam; Melker, Hester de; Rümke, Hans; Hak, Eelko; van Hoek, Albert Jan (2018): Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. In PloS one 13 (2), e0192640. DOI: 10.1371/journal.pone.0192640.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	This study reports some parts of the economic evaluation in great detail, especially parts about incidence and mortality data, but has a very simple costing and QALY part. Only indirect costs are considered and split into IPD and CAP. The values for those cost and QALY parameters are taken from another modeling study. The study does not take the full possibility of age-stratified effects into account. Indirect effects are taken into account and an alternative scenario for childhood vaccination is analyzed.	**1** ☐ **Many gaps/ inconsistent** **2** ☐ **3** ☒ **4** ☐ **Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The model population is stratified into age groups "60-64", "65-69", "70-74", "75-79", "80 plus" and size of the age groups are given that suggest, that the study aims at the general population. Risk groups or risk factors are not mentioned.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Several alternative strategies to the current scheme (no vaccination for elderly) to vaccination of elderly at age 60/65/70 with PCV13 and/or PPSV23 with and without re-vaccination. Additionally, switching infant vaccination from PCV10 to PCV13 was explored. *Vaccine uptake:* 50% uptake for elderly was assumed as well as 100% uptake for children for all vaccinations, respectively. Administration of the vaccines was modelled at the model start and scenario analyses have been carried out for different age groups starting with age 60/65/70.	

3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The model is described as a static model and no illustration of the model is given. There is no information about the cycle length, also a yearly time step can be assumed. Disease states are not clearly identified, although IPD and CAP can be assumed to be the modelled health states. Costs and utilities are attributed to these two disease states.
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The intervention strategies are compared to the current vaccination scheme for elderly, which is no vaccination, and under the consideration of childhood/infant vaccination with PCV10. The rationale for the comparator is stated.
5	Perspective	Are the perspective of analysis and its rationale stated?	The analysis is performed from the perspective of a health care provider following national guidelines. No other perspectives have been explored in further analyses.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The analysis is conducted as a cost-effectiveness analysis giving incremental costs per incremental QALY. Prevented cases and prevented deaths are also reported in the results section but are not included in the cost-effectiveness results.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	*Incidence:* Incidence estimates are based on Dutch national surveillance data from 2004 to 2015, for the different serotypes of the vaccines. Serotype prevalence is projected using six assumptions: 1. IPD incidence of PCV7 types remains stable 2. IPD incidence of (PCV10-PCV7) serotypes will decline for 5 more years and then drops to 0.8/100,000 3. IPD incidence of (PCV13-PCV10) serotypes remains stable for current childhood vaccination. It will decline for the scenario of PCV13 infant vaccination. 4. IPD incidence of (PPSV23-PCV13) serotypes will continue to increase (serotype replacement) 5. IPD incidence of non-PPSV23 serotypes will continue to increase (serotype replacement) 6. Overall IPD incidence will increase (by estimated linear trend of PPSV23 and non PPSV23 serotypes) to the pre-PCV level of 2005/06 of 54/100,000 among 60plus year old. *Vaccination related parameters:* *Efficacy:* PCV13 IPD: 75% Non-IPP: 38% (no age-stratification) PPSV23 IPD: 64% Non-IPP: 19.6% (no age-stratification) *Waning:* Linear reduction in waning is assumed for PCV13 and PPSV23 for IPD and CAP. PCV13 reduced to 0% VE after 15 years for both IPD and CAP, respectively. PPSV23 reduces to 0% after 6 years. Concrete values are given in Figure 1. *Years in full protection:* PCV13 provides 10.0 years in full protection for IPD and 10.03 years for CAP. PPSV23 provides 3.5 years in full protection for IPD and 3.55 years for CAP. *Costs:* Costs are €14,584 for IPD and €7,872 for CAP. No further stratification is provided. *Utilities*: QALY loss is 0.0709 for IPD and CAP, respectively.
8	Time	Is the time horizon reported?	The time horizon is 10 years in the base case. 5, 15 and 50 years and an “unlimited” (life-long) scenario are explored in the

	horizon		sensitivity analyses.
9	Discount rate	Is the discount rate reported?	Costs are discounted at 4.0% and health benefits with 1.5%.
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Deterministic, univariate sensitivity analyses have been performed on: • assumptions on vaccine effectiveness, • age at vaccination • mortality assumptions • cost assumptions • adding administration costs • QALY assumptions • discounting • time horizon • the level of herd protection generated by the infant programme No probabilistic sensitivity analysis is performed. No ranges for the deterministic sensitivity analyses are given.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	Results are reported for Cases, Cases Prevented, Deaths, Deaths Prevented, QALYs, QALYs gained and Cost Savings. Cost-effectiveness estimates are given for different ages at vaccination and time horizons. The most cost-effective strategy is a single vaccination of PPSV23 at the age of 70 years with an ICER of €6,201/QALY.

Relevance and validity of economic evaluation

Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The study is relevant, but in many cases, there are unnecessary simplifications in the model, i.e. ignoring age specific data, no prices-resources framework and arbitrary scenario/sensitivity analyses.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☒** **4 ☐ High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	The study does explicitly state that it models the general population, although this can be assumed. The model is stratified by age, but vaccine efficacy, costs and utilities are not age-specific. Only the different mortality-parameters are age-specific. Sources of population sizes, background mortality/life-expectancy are also not clearly stated. The population does not match the trial population and age-specific results from the trial are not incorporated.	
2	Intervention	Are assumptions/design regarding interventions (dose	The study evaluates different strategies of vaccination of the elderly against IPD and CAP without further stratification. The	

	and setting	and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	authors state that the adult vaccine uptake (50%) to be based on the corresponding value for influenza without sources and assume 100% vaccination uptake for pneumococcal infant vaccine although the cited source says 93.6%. Different ages for starting the elderly vaccination are explored with the same assumptions about uptake.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	Only IPD, CAP and death are included in the model without further stratification. IPD mortality is age- and vaccine-type specific from the Dutch surveillance data. CAP mortality is taken from a German source. The probability of the three health states is influenced by direct effects from the elderly vaccination and indirect effects from infant vaccination.
4	Comparator	Does the choice of comparators reflect current practice?	The different vaccination strategies are compared to infant vaccination with PCV10, which is the current practice in The Netherlands.
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The analyses are performed from a health care provider's perspective and no other perspective is explored in the sensitivity analyses. The authors state, that a societal perspective is usually applied in the Netherlands, but do not give reasons, why they did not consider this perspective. No guidelines are mentioned in this context. The cost components are taken from another Dutch study (Mangen et al.[2]), but no detail is given in this study which cost components are used. No age-specific costs are used. Administration costs are omitted. No reference year of the costs is stated.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	QALY losses are estimated to be identical for IPD and CAP (0.0709) and another model has been referenced as the source. No other information is provided about the values of population norms, the duration of the health states or the utility decrements. It is stated, that population norms are used in the calculation of QALYs.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	Incidence is stratified by age and the probability of IPD and CAP were age-specific and data obtained from the Dutch (registry) data. Age-stratified IPD mortality is based on the Dutch surveillance data and CAP mortality from a German study. Background mortality is taken from a survival curve (without reporting the source). Indirect effects were modelled on 6 different assumptions listed in (7) in the first part. Not all assumptions are backed by data or literature. The study applied PCV13 vaccine efficacy from the CAPITA study, without using age-specific effectiveness. PPSV23 effectiveness is taken from a meta-analysis by Falkenhorst et al. (2017)[32] and waning from Andrews et al. (2012)[13]. Another CEA study is cited for costs and QALYs.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	The time horizon is 10 years, but extensive sensitivity analyses have been conducted on different time frames to capture all relevant effects.
9	Discount rate	Is the recommended discount rate applied?	A discount rate of 4.0% for costs and 1.5% for QALYs is applied as recommended by national guidelines.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	Sensitivity analyses are performed for vaccine effectiveness, age at vaccination, mortality assumptions, cost assumptions, adding administration costs, QALY assumptions, discounting, time horizon and the level of herd protection generated by the infant programme. The ranges of the different analyses are described in table 6 in the results section, but it is questionable, if it is plausible to explore "no mortality" scenarios. There are no other sources or rationales for the ranges applied in the sensitivity analyses. No rationale given for the omission of probabilistic sensitivity analysis.

11	Conclusion	Are conclusions supported by results?	The study concludes a PPSV23 single dose vaccination of elderly between 60 and 70 to be the most cost-effective strategy. All ICERs lie beneath a threshold of €50,000/QALY and most strategies are beneath €20,000/QALY

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** Belgium			**Study:** Willem, Lander; Blommaert, Adriaan; Hanquet, Germaine; Thiry, Nancy; Bilcke, Joke; Theeten, Heidi et al. (2018): Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. In Human vaccines & immunotherapeutics, pp. 1–12. DOI: 10.1080/21645515.2018.1428507.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	The study analyses the cost effectiveness of several vaccination strategies involving PCV13 and PPSV23 compared to the current state, PPSV23 alone. The study uses a multi-cohort Markov model for persons above 50 years incorporating indirect effects from childhood vaccination. PCV13 effectiveness is based on CAPITA-data and waning is assumed to start after 5 years with a logistic reduction to 50% after 10 years. PPSV23 effectiveness is based on Andrews et al. 2012.	**1 ☐ Many gaps/ inconsistent** **2 ☐** **3 ☐** **4 ☒ Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	General population in Belgium above 50 years stratified into the age groups “50 to 64 years”, “65 to 74 years”, “75 to 84 years”,”≥85 years”, no specified risk groups, one cohort of the year 2016 taken from demographic statistics from Eurostat 2015.	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Table 1 lists the current treatment regime (PPSV23) in 2015 and the vaccine uptake for different scenarios. This includes: PPSV23 and/or PCV13 vaccination with and without re-vaccination, respectively. However, there is no clearly stated list/enumeration of the different scenarios. *Vaccine uptake:* Current situation: 0.79% (50-65y) 2.46% (65-74y) 3.01% (75-84y) 2.48% (85-105y) Intervention scenario: 25% (50-65y) 50% (65-74y) 60% (75-84y) 40% (85-105y) Re-vaccination scenario: 15% (50-65y) 25% (65-74y) 25% (75-84y) 20% (85-105y)	
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The model type is a multi-cohort static model. Figure 3 contains the model diagram. It is not entirely clear how to categorize the model, but it can be assumed that it is a markov model of cycle length of one year. Input parameters are found in Appendix E. The disease states are IPD cases, further stratified by pneumonia, meningitis and other IPD with meningitis cases possibly showing hearing loss or neurological sequelae. Non-invasive pneumococcal pneumonia is also considered and stratified by inpatient and outpatient treatment. Death is an additional health state. Costs and utilities are given per disease state.	

4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	Comparator is the current (2015) vaccination schedule for adults in Belgium, which consists of PPSV23 vaccination in elderly with low vaccination coverage.
5	Perspective	Are the perspective of analysis and its rationale stated?	Perspective is the health care payer's perspective according to national guidelines. No other perspectives are explored.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	The study is conducted as a cost-effectiveness study using QALYs as the main outcome, but a range of other outcome parameters are evaluated as well (Key outputs include: averted hospitalized invasive pneumococcal pneumonia, meningitis, other IPD, hearing loss and neurological sequelae from meningitis, outpatient and hospitalized non-IPP cases and fatalities.).
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	There is a 35-page long appendix, which lists all the parameters used in the model from page 23 to page 31 and giving their sources. *Incidence:* Incidence is based on data from the National Reference Centre (NRC), 2015, INTEGO 2013 R81 and pooled estimates from Capelastegui et al and Holm et al. *Vaccination related parameters:* *Efficacy:* PCV13 IPD: 50-84 years: 75.5% [47-90%]; ≥85 years: 0% Non-IPP: 50-84 years: 41.1% [12.7-62%]; ≥85 years: 0% PPSV23 IPD: 50-84 years: 56% [40-68%]; ≥ 85 years: 0% Non-IPP: 50-84 years: 30.8% [31-52%]; ≥85 years: 0% *Waning:* PCV13: a logistic waning function with parameter k = 0.75 and mid-point of 10 years. PPSV23: an exponential waning function with mid-point of 1.5 years. *Years in full protection:* PCV13: 9.54 years (IPD & non-IPP) PPSV23: 2.29 (IPD & non-IPP) *Serotype Coverage:* PCV13 25% (IPD & non-IPP) PPSV23 66% (IPD), 51% (non-IPP) A full list of included unit cost prices is provided Aggregating categories of the unit cost prices are the health states. Costs are not divided into resource use and prices. The sources are given Utility estimates are reported with sources.
8	Time horizon	Is the time horizon reported?	The model used a life-long time-horizon and costs and outcomes have been calculated until the last intervention cohort had died. The time horizon is not subject to sensitivity analyses.
9	Discount rate	Is the discount rate reported?	The discount rate in the base case is 3% for costs and 1.5% for outcomes.

10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Sensitivity analyses are reported in appendix C (page 11 to 21 in the supplement) and include deterministic, uni- and multivariate as well as scenario and probabilistic sensitivity analyses. Univariate sensitivity analysis is performed on: • Higher PPV23 protection against non-IPP • Five years of PCV13 protection followed by no protection • Minimum/Maximum duration of PCV13 protection • Age-independent PCV13 efficacy in all ages between 50-84 year old • Two years of complete PPV23 protection followed by no protection • Five years of PPV23 protection without waning • Five years of both PCV13 and PPV23 protection without waning • Minimum/Maximum serotype shift • Quick/Slow serotype relapse • Higher hospitalized pneumococcal pneumonia incidence • Higher percentage of pneumococcal pneumonia in outpatient CAP • PCV13/PPSV23 price reduction • Higher PPV23 vaccine efficacy Multivariate SA consists of combinations of the above, while the results of the PSA are presented as CEAFs. Ranges for PSA cannot be found for all parameters and values of the distributions for PSA are only reported for the incidence of pneumonia and the case fatality ratio.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	Appendix B (pages 5 to 10) lists comprehensive tables on the different components (costs and effectiveness). Mean ICER of €201,172/QALY for PCV13 compared to the current situation (low PPSV23 in adults). Cost categories are Total Medical Costs (discounted/undiscounted), Total Vaccination Costs, QALY (discounted/undiscounted), ICER

Relevance and validity of economic evaluation

Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The model has a relevant study question and considers all relevant health states. If parameter values are taken from other countries, they are usually neighboring countries. Sensitivity analyses are conducted on a wide range of parameters, but not all ranges have been reported.	**1 ☐ Low relevance/ validity** **2 ☐** **3 ☐** **4 ☒ High relevance/validity**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the	The target population (general population, 50 years+; age groups “50 to 64 years”, “65 to 74 years”, “75 to 84 years”,”≥85 years”) is relevant and represents the intended target group of the intervention. But it does not coincide with the study population in CAPITA nor with the PPSV23 effectiveness study population of Andrews et al. (2012). Demographics are based on national data from Eurostat.	

		treatment is envisioned to be used?	
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates adult pneumococcal vaccination against inpatient IPD, (IP pneumonia, Meningitis, Other IPD) – and CAP (inpatient, outpatient). Coverage rates are based on observed rates in the national influenza vaccination program.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The following health events are included: (I) IPD in the form of IP pneumonia Meningitis, other IPD and (II) non-IPP stratified by inpatient and outpatient care. For meningitis, long-term effects of hearing loss and neurological sequalae are considered and death may occur from any state. The events are mutually exclusive. Vaccine failure is considered in the model structure.
4	Comparator	Does the choice of comparators reflect current practice?	The different scenarios are compared to the current PPSV23 vaccination for elderly under the consideration of childhood vaccination.
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The perspective is the perspective of the health care payer and is demanded by national guidelines. The direct health care costs are given as per-event-total costs and no prices-resources framework is used. The costing of the events is not comprehensively described and thus assessing its validity is difficult. Following from the perspective, indirect costs are not considered.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	QALYs are used as the primary outcome. Utilities are taken from a French study and decrements have been subtracted from the age-specific population norm. QALY losses are calculated for hospitalizations, non-hospitalized pneumonia and long-term consequences of meningitis, i.e. the do not correspond to the exact health states modelled.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use, unit costs)? Are assumptions valid?	Incidence data and serotype distribution are taken from the Belgian National Reference Center and serotype distribution was adopted from Germany. A Danish study (Benfield et al.) are used to calculate the distribution of non-IPP serotypes. Pneumonia incidence is estimated from data of a primary care network (INTEGO) and complications and mortality from hospital data. All-cause mortality is based on national statistics. Indirect effects are based on SPIDNET data, a pooled analysis from 10 European countries (Hanquet et al. 2016). The study applied age un-specific vaccine effectiveness from the CAPITA study for PCV13 and Andrews et al. for PPSV23. It explores age-stratification in the sensitivity analyses. However, it is not described how the hazard ratio of 1.058 per year of age for the vaccine efficacy has been derived, which has been applied to the effectiveness of PPSV23 in a scenario analysis. Besides utility decrements and the above mentioned sources, most input parameters are informed by Belgian sources.
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	The discount rate complies with the cited guidelines.

10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	Given ranges seem plausible, but ranges are not given for all parameters.
11	Conclusion	Are conclusions supported by results?	The results are mainly reported in the context of cost-effectiveness acceptability frontiers. The conclusion is in line with the results, stating that for a WTP of €50,000 per additional QALY the current strategy of PPSV23 is cost-effective.

EVIDEM instrument – Assessment of quality of economic evaluations (adapted)				
Disease: Invasive and non-invasive pneumococcal diseases **Intervention:** Pneumococcal polysaccharide vaccine (PPSV23); Pneumococcal conjugate vaccine (PCV13) **Setting:** Germany			**Study:** Kuchenbecker, Ulrike; Chase, Daniela; Reichert, Anika; Schiffner-Rohe, Julia; Atwood, Mark (2018): Estimating the cost-effectiveness of a sequential pneumococcal vaccination program for adults in Germany. In *PloS one* 13 (5), e0197905. DOI: 10.1371/journal.pone.0197905.	
Completeness and consistency of reporting economic evaluation				
Type of evidence		**Question**	**Rationale**	**Score**
Economic evaluation		Are all the dimensions of the economic evaluation reported? Is the reporting complete and transparent? Are estimates used in analysis in agreement with clinical literature/data? Are estimates used consistent with sources? Is information consistent across sections of study report/publication (abstract, methods, results, discussion)? *See dimensions below*	The study analyses the cost-effectiveness of several vaccination strategies involving PCV13 and PPSV23 compared to the current state from the payer' and societal perspectives. It adopts an earlier developed US microsimulation framework with Markov-type process by Weycker et al (2012). All dimensions but discounting are reported. The VE data for PCV13 comes from the CAPITA study and VE for PPSV23 is based on the previous estimates by an expert panel. The study shows inconsistency in the reporting the methods applied to estimation of the waning rate and calculation of herd effects. The representation of the applied parameters for PSA is not intuitively interpretable. The results are reported in detail.	**1 ☐ Many gaps/ inconsistent** **2 ☒** **3 ☐** **4 ☐ Complete and consistent**
	Dimension	**Question**	**Comment**	
1	Target population	Is the target population for this intervention defined?	The target population is defined as the German population aged ≥ 18 years. The population is stratified by health risk (high, moderate, low) and single age increment. The definition of the risk groups is given. The percentages assigned to each risk group are given for the age groups: 18-59 y.o, 60-64y.o, 65-74y.o, 75-99 y.o. • Low-risk: "immunocompetent patients without any chronic medical conditions"; • Moderate-risk: "immunocompetent patients with at least one chronic medical condition"; • High-risk: "immunocompromised/immunosuppressed patients, with or without chronic medical conditions (congenital or acquired)".	
2	Intervention and setting	Are intervention & setting described (dose, duration, mode of delivery, hospital specialist, etc)?	Intervention: 7 vaccination scenarios vs current practice. The vaccination scenarios are defined for the risk groups and age groups: 18-59 y.o., 60-65y.o., 66-99y.o. The study defines sequential vaccination as a strategy with initial vaccination with PCV13, followed by PPSV23 after 6-12 months and revaccination every 6 years afterwards.	

			3 hypothetical scenarios include: • sequential vaccination for all but low-risk 18-59y.o. people • 60-65y.o., 66-99y.o. in low-risk group with PPSV23 (current policy) and people at high- and middle risk groups with the sequential strategy • 18-59y.o. in middle risk, and 60-99y.o. in low- and moderate risk groups are vaccinated with PCV13 and all rage groups in high risk group are vaccinated with the sequential strategy Other 4 scenarios are evaluated in SA Vaccination rate fall all strategies is 31.4% which is observed for the current policy. Revaccination rate is assumed to be 100% (tested in SA).
3	Model & event pathway	Is the model described (model diagram/figure preferred), with details of the event pathway & attribution of costs to each node/part/arm/option/branch of the model?	The model is briefly described. A descriptive figure is given in the main text. The model type is described as a static incidence model with a microsimulation framework with Markov-type process which was adopted from an US study by Weycker et al (2012)[15]. The cycle length is 1 year. The outcomes are produced for each modeled individual. The modeled events include diseases (IPD: bacteremia and meningitis; nIPD: non-bacterial pneumonia in-and outpatient) and death. The costs depend on the disease. The study performs 1,000 simulations in each scenario.
4	Comparator	Are comparators described? Is the rationale for comparator selection stated?	The analysis is performed in comparison with the current policy. The current policy is vaccination with PPSV23 of all elderly (≥60) and adults ≥16 with at least one chronic disease not associated with immune suppression and a sequential vaccination (PCV13 initial, followed with PPSV23) for adults at high risk.
5	Perspective	Are the perspective of analysis and its rationale stated?	Two perspectives are taken: Statutory Health Insurance and societal.
6	Type of analysis	Is the type of analysis stated? Is the rationale for outcomes selection (effectiveness measure or utilities) stated?	Cost-effectiveness analysis of alternative scenarios of pneumococcal vaccination with PCV13 and/or PPSV23 compared to the current practice. The outcomes of the analyses are: number of cases prevented, LYG, QALY, costs. Cost-effectiveness is estimated as cost per QALY gained and cost per LYG.
7	Parameters and estimates	Are all the parameters used in the model (effectiveness data, adverse-event data, resource use, unit costs, health states, utilities) and their sources reported? Are the methodologies to obtain parameter estimates described (e.g., does it include currency conversion, inflation adjustments, calculation of transition probabilities, expert panel data, etc…)? Are all assumptions listed? Are estimates consistent with sources cited?	The parameters are listed in the main text and the supplemental material. *Incidence:* The applied incidence rates are reported with the respective sources. The rates are age- and risk group stratified. The rates are given for all modelled diseases: meningitis and bacteremia (IPD) and inpatient- and outpatient non-bacteremic pneumonia (nIPD). Inclusion of the herd effects of the paediatric vaccination with PCV13 is described. The maximum reduction in % due to herd effects is calculated based on prediction of serotype distribution in IPD performed using unpublished serotype-specific IPD data from the National Reference Laboratory (NRZ) on Streptococcal Diseases. The observed effects are extrapolated over the next 5 years based on predicted serotype distribution in IPD. The prediction of the serotype distribution is performed using a model showing the best fit to the data observed over 5 years (2010/11-2015/16). The study does not report the method used to obtain cumulative herd effects by year of modelling from the predicted serotype distribution. Table S2 shows the applied values, which illustrate a significant jump from 0% to approx. 80% in the modelled year 2. This trend is not discussed in the paper. Cited bibliography in the respective supplemental tables is not reported. Case-fatality- and general mortality rates are reported with the cited references. *Vaccination related parameters:* *Efficacy:* PCV13: The values for the VE parameters are obtained from the CAPITA study. Serotype coverage PCV13 against IPD is assumed to be 29.3%. PCV13 VE against IPD for immunocompromised is taken as 78% of VE for people of the low and

<table>
<tr><td></td><td></td><td></td><td>moderate risk. PCV13 VE against nIPD for immunocompromised is taken as 65% of VE for people of the low and moderate risk.
PPSV23: The values for the VE against IPD parameters are obtained from Smith et al. (2008) [16]for immunocompetent and Shapiro et al. (1991)[33] for (immunocompromised) individuals. PPSV23 VE against nIPD is assumed to be 0%.
The approach is described in the supplement.
The study reports in the main text the VE values by health risk group and by age group: 18-49y.o.,50-59 y.o.,60-64 y.o.,65-74 y.o.,75-99 y.o.

<table><tr><td>VE</td><td>18-49y.o.</td><td></td><td>50-59 y.o.</td><td></td><td>60-64 y.o.</td><td></td><td>65-74 y.o.</td><td></td><td>75-99 y.o.</td><td></td></tr><tr><td>PCV13:</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td></tr><tr><td>ag IPD</td><td>85%</td><td>66%</td><td>82%</td><td>64%</td><td>80%</td><td>62%</td><td>77%</td><td>60%</td><td>70%</td><td>55%</td></tr><tr><td>ag nIPD</td><td>4%</td><td>3%</td><td>4%</td><td>3%</td><td>4%</td><td>3%</td><td>4%</td><td>3%</td><td>4%</td><td>2%</td></tr><tr><td>PPSV23 ag IPD</td><td>93%</td><td>21%</td><td>88%</td><td>15%</td><td>83%</td><td>8%</td><td>76%</td><td>2%</td><td>64%</td><td>0%</td></tr></table>*Waning:* VE rates are for years since vaccination. VE of both vaccines wanes over 15 years. VE of PPSV23 is assumed to wane starting with the 1st year, PCV13 is assumed to show stable protection over the first 5 years.
The waning rates are estimated based on published literature.
Methods for the estimation of the waning of PPSV23 VE for the immunocompromised people are no reported.
The approach is inconsistently described:
the main text reports estimation of an exponential function, whereas in the supplement it is stated that the rates are obtained using a linear interpolation based on the values obtained from Smith et al (2008)
Table 2 represents VE rates aggregated by age- and health risk groups. The table shows the vaccine effectiveness over time, although in in text it is stated that “the values represent percentage of decline in corresponding year from prior period”.
The rate of PCV13 waning is 50% of the rate of PPSV23 waning but is applied first after the initial 5year period of constant protection.
We calculated years of full protection and average duration of protection with PCv13 ag IPD and nIPD, PPSV23 ag IPD:
To note, these calculations were based on the values of VE given in Table 2 of the main text. Table 2 shows inconsistency in the reporting of the values of VE for PCV13 ag IPD in the low risk group of 65-74 y.o., for year 10 (VE =1%) and for PPSV23 ag IPD for high risk group of 50-59y.o. for year 10 (VE =37%, though initial VE =15%)
<table><tr><td>VE</td><td>18-49y.o.</td><td></td><td>50-59 y.o.</td><td></td><td>60-64 y.o.</td><td></td><td>65-74 y.o.</td><td></td><td>75-99 y.o.</td><td></td></tr><tr><td>PCV13:</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td><td>low/mod</td><td>high</td></tr><tr><td>ag IPD</td><td>12.7y</td><td>9.9y</td><td>12.2y</td><td>9.5y</td><td>11.3y</td><td>8.8y</td><td>8.3y</td><td>8y</td><td>8.3y</td><td>6.5y</td></tr><tr><td>ag nIPD</td><td>0.6y</td><td>0.45y</td><td>0.6y</td><td>0.45y</td><td>0.6y</td><td>0.45y</td><td>0.55y</td><td>0.35y</td><td>0.4y</td><td>0.25y</td></tr><tr><td>PPSV23 ag IPD</td><td>10.2y</td><td>2.8y</td><td>11.1y</td><td>3.8y</td><td>11.7y</td><td>1.35y</td><td>11.7y</td><td>0.29y</td><td>10.1y</td><td>0y</td></tr></table>
Costs and Health outcomes:
The applied costs are reported per case for each modeled disease and age-group. Medical costs include hospitalization- and outpatient costs. Non-medical costs comprise of work-loss days and costs due to productivity loss. The sources are stated.
Utility estimates by age and health-risk groups are reported with sources.</td></tr>
<tr><td>8</td><td>Time horizon</td><td>Is the time horizon reported?</td><td>The time horizon is reported and is modeled as until death or 100 years of age.</td></tr>
<tr><td>9</td><td>Discount</td><td>Is the discount rate reported?</td><td>The discount rates are not reported.</td></tr>
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	rate		
10	Sensitivity analyses	Are sensitivity analyses reported? Are rationales for selection of parameters and ranges used in sensitivity analyses reported?	Sensitivity analyses are described in the main text and include univariate- and probabilistic SA. The parameters with the taken distributions are stated in the supplemental material. Univariate sensitivity analysis is performed on: • assumption of PCV13 constant protection over 5 years • PPSV23 effectiveness against all-cause NBP of 64% • revaccination rate of 50% in 2 vaccination scenarios Parameters for PSA are reported for incidence, effectiveness of PCV13 and PPSV23, mortality and medical costs. The PSA is shortly described only in the main text. The study reports the applied distributions. The table with the PSA parameters is not described and methods for application of the stated parameters are not reported making it difficult to assess completeness and consistency of the information. The sources are numbered but not reported in the respective supplemental material making it unclear what bibliography is cited.
11	Results	Are disaggregated results reported (cost & effectiveness per component, direct and indirect costs, total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios)?	The results of base case scenarios are reported. For resulted ICERs the study presents a scatterplot. The reported costs are divided into medical-, non-medical and vaccination cost. The major outcomes are given also per patient for each evaluated scenario. The results are reported also for all adults, adults <60 years old and ≥60 years old. The ICER per LYG ranged from €3,662 to €23,061 (payer) and €3,258 to €29,617 (societal). All scenarios but one are considered to be cost-effective.

Relevance and validity of economic evaluation

Type of evidence	**Question**	**Rationale**	**Score**
Economic evaluation	Is the study question relevant (choice of comparator, time horizon, patient population, outcome, perspective)? Is the design appropriate? (how close to real disease progression, costs included, strength of assumptions, sensitivity analyses, quality of sources (clinical, costs, epidemiology, utilities)? *See dimensions below*	The study applies relevant comparator, time horizon, perspective, targeted population, outcomes and costs. Due to incompleteness in reporting it is difficult to assess plausibility and relevance in the important dimensions of the study. The event pathway applied in the model is not described in detail. The study refers to four sources which are used to derive incidence rates without reporting the methods of how the data is adjusted making it difficult to assess the relevance. The study lacks description of methods for calculation of cumulative herd effects from the reported predicted serotype-distributions in IPD by that making it difficult to assess relevance of applied herd effects. It is not clear how the applied values of the herd effects for nIPD are obtained. Applied PPSV23 VE is based on the estimates by a Delphi expert panel. Report on applied discounting is missing. Reporting of the ranges applied in the PSA is not complete and the table is not easy to interpret. Uncertainty of the assumption that PCV13 VE is 50% of the values of PPSV23 VE applied in extrapolations to calculate age-specific PCV13 VE values and waning rates is not tested.	**1 ☐ Low relevance/ validity** **2 ☒** **3 ☐** **4 ☐ High relevance/validity**

	Dimension	**Question**	**Comment**	
1	Target population	Is the target population relevant (age, gender, disease stage, co-morbidities, etc…)? Is it comparable to the	The modeled population is a hypothetical cohort of German adult population aged 18 years and older stratified by health risk groups and one-year age increments. The modeled population is relevant for the evaluated intervention but does not correspond	

		trial/study population in which efficacy/effectiveness data was obtained? Does it correspond to the actual population in which the treatment is envisioned to be used?	to the population of the CAPITA trial (≥65y.o) based on which PCV13 VE parameters are derived. Population size estimates are obtained from official data of the Federal Health Monitoring of 2012. The division of the population on the risk groups is based on the data from published observational studies conducted in Germany and on the unpublished data "from the InGef (former Health Risk Institute)".
2	Intervention and setting	Are assumptions/design regarding interventions (dose and duration, mode of delivery) & setting (hospital/community, country, etc) valid with respect to the indication/proposed coverage & clinical context?	The study evaluates adult pneumococcal additional vaccination strategies against inpatient IPD (meningitis and bacteremia) and NBP (inpatient, outpatient). The coverage rate is based on observed current uptake under the current vaccination policy.
3	Event pathway	Does the model reflect a realistic event pathway according to current knowledge?	The developed model includes following events: model entry, vaccination, disease in form of IPD and nIPD, death. For meningitis, long-term effects of hearing loss and neurological sequalae are not considered. The model is not described in detail making it difficult to assess the event pathway.
4	Comparator	Does the choice of comparators reflect current practice?	The different scenarios are compared to the current PPSV23 vaccination for elderly issued by the German standing committee for vaccination (STIKO). The current recommendation comprises of "PPSV23 for all elderly (≥60) and all patients ≥16 with at least one chronic disease not associated with immune suppression. For all other patients at risk (high-risk representing (congenital or acquired) immunocompromised/immunosuppressed patients, with or without chronic medical conditions), sequential immunization with PCV13 first is recommended, followed by PPSV23. Repeated vaccination with PPSV23 is recommended for patients in all risk groups. Elderly are recommended revaccination every 6 years with PPSV23 following individual assessment by the physician".
5	Perspective and costs	Is the perspective chosen valid? Are all relevant costs considered (intervention, healthcare professional visits & procedures, hospitalization, long-term care, lab tests)? Are assumptions for cost selection valid?	The taken perspectives are of the health care payer and societal as suggested by the "German Recommendations on Health Economic Evaluation: Third and Updated Version of the Hanover Consensus"[20]. The direct health care costs are divided into hospitalization and outpatient costs given per case and stratified by the age-group. The costs are derived from national tariff manuals. Inpatient costs are estimated using DRG specific calculations using data from the Institute for the Hospital Remuneration System (InEK) (reference of 2013). Outpatient costs comprise of physician costs (per case) and medication costs. The costs per unit are not reported. Calculation of vaccination costs are made using pharmacy retail price of a package size of ten for PCV13 (62.93 €/dose) and PPSV23 (28.32 €/dose) (of 2018). For the societal perspective, the indirect costs are derived based on number of sick-leave days (of 2012) and the value of a single sick-leave day (of 2014). There is not information of what year is chosen to be the reference.
6	Outcome measures	Are the selected outcomes measures (efficacy, safety and patient reported outcomes [PRO]) relevant? Are the primary efficacy/effectiveness measures used, and major side effects included? Are instruments to estimate PRO valid? Are assumptions for outcomes selection valid?	QALYs and LYG are used as the primary outcomes. Utilities for the general German population are given by age- and risk-group and obtained from a German study which examines and compares cross-section surveys. Disutilities originate from published cost-effectiveness studies of pneumococcal vaccination in England and Wales and USA. Reduction utilities due to disease is given as one value for IPD and another value for all-cause NBP, the parameter is not age-group or risk-group specific.
7	Parameter estimates	Are the sources and methods used to estimate the parameters solid (effectiveness data, adverse event probabilities, health states, PRO, utilities, resource use,	*Incidence.* IPD incidence rates are derived based on the data of a publication on IPD in North-Rhine Westphalia Germany by Reinert et al. (2005)[34] extrapolating the incidence of the overall population; health-risk adjustment is based on van Hoek et al. (2012)[23].

		unit costs)? Are assumptions valid?	The study refers to four sources which are used to derive incidence rates without reporting the methods of how the data is adjusted making it difficult to assess the relevance. Indirect effects of the pediatric vaccination with PCV13 are included into the study. The herd effects are major effects considered in the study. The methods are not thoroughly described, a rationale is not provided. For the IPD incidence the study reports cumulative herd effects expressed in % for each modelled age-group for the first 5 years assuming 100% of the herd effects reached in the 5th year and keeping absolute maximum herd effects constant for the modeled time horizon. The reported rates show that the cumulative herd effects reach over 80% by year 2 in all age groups but 75-99y.o. These percentages are derived from projections of serotype distributions in IPD. Regarding these projections, although the non-liner model applied to project the serotype distribution and it results are reported, the methods of how the reductions in the IPD incidence are derived from these results are not reported. Given the ways the information is reported it is difficult to assess its validity. The herd effects for NBP are obtained from published study by Pletz et al (2016) [35]. *Vaccine Effectiveness*. The values for the PPSV23 VE for the individuals of the low- and moderate risk are obtained from the estimates by Delphi expert panel reported by Smith et al. (2008) [16]. Smith et al. (2008) report estimated PPSV23 VE values for healthy individuals by age group 50-64y.o., 65-79y.o., 80y.o. The study applies a linear interpolation to estimate the VE values for age-year increment anchoring the VE values given by Smith et al. (2008) to age 50, 65 and 80 years: 93%, 80% and 67%. The waning rates estimates are taken from the same source by Smith et al (2008) and are linearly interpolated by age increment and modeled year. For the immunocompromised people of age 18-68 y.o. the study obtains the estimate (21%) reported in a controlled study by Shapiro et al (1991) who also state that the resulted estimate is not statistically significant. For 51-68 year olds the VE estimate is extrapolated by interpolating between the two data points: 21% for 50y.o. and 0% for 69y.o. For the immunocompromised people of age ≥69 y.o the VE is assumed to be 0%. Methods for the estimation of the waning of PPSV23 VE for the immunocompromised people are no reported. The values for the PCV13 VE against IPD and nIPD are estimated based on the reported VE estimates in the CAPITA study. Based on the average age of 73y. of the participants in the trial, the resulted VE of 75% against IPD and 45 against nIPD are assigned to persons aged 73y. The VE values for younger and older age are obtained using extrapolation by age-year increment. The extrapolation is performed using the age-specific differences of PPSV23 VE resulted from the interpolation and applying 50% of these differences for PCV13. PCV13 protection against IPD is assumed to be constant for 5 years and then to wane with the rate of 50% of the corresponding PPSV23 waning rates by year increment (setting the year 5 as the first year when the waning starts).
8	Time horizon	Is time horizon long enough to capture all meaningful differences in costs and outcomes between the intervention and comparator? Are assumptions used valid?	Applied lifetime horizon is long enough to capture all meaningful differences in costs and outcomes.
9	Discount rate	Is the recommended discount rate applied?	The discount rates are not reported.
10	Sensitivity analyses	Do sensitivity analyses cover the most critical parameters within a valid range?	Given ranges applied in the univariate SA seem plausible. Not comprehensive reporting of PSA parameters and absence of the bibliography make it difficult to assess plausibility of the applied ranges.
11	Conclusion	Are conclusions supported by results?	The conclusion is in line with the results that most of the evaluated strategies are cost-effective.

References

1. Jiang Y, Gauthier A, Annemans L, van der Linden M, Nicolas-Spony L, Bresse X. Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. Expert Rev Pharmacoecon Outcomes Res. 2012;12:645–60. doi:10.1586/erp.12.54.
2. Mangen M-JJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46:1407–16. doi:10.1183/13993003.00325-2015.
3. Blommaert A, Bilcke J, Willem L, Verhaegen J, Goossens H, Beutels P. The cost-effectiveness of pneumococcal vaccination in healthy adults over 50: An exploration of influential factors for Belgium. Vaccine. 2016;34:2106–12. doi:10.1016/j.vaccine.2016.03.003.
4. Rodriguez Gonzalez-Moro JM, Menendez R, Campins M, Lwoff N, Oyaguez I, Echave M, et al. Cost Effectiveness of the 13-Valent Pneumococcal Conjugate Vaccination Program in Chronic Obstructive Pulmonary Disease Patients Aged 50+ Years in Spain. Clin Drug Investig. 2016;36:41–53. doi:10.1007/s40261-015-0345-z.
5. Stoecker C, Kim L, Gierke R, Pilishvili T. Incremental Cost-Effectiveness of 13-valent Pneumococcal Conjugate Vaccine for Adults Age 50 Years and Older in the United States. J Gen Intern Med. 2016;31:901–8. doi:10.1007/s11606-016-3651-0.
6. van Hoek AJ, Miller E. Cost-Effectiveness of Vaccinating Immunocompetent /=65 Year Olds with the 13-Valent Pneumococcal Conjugate Vaccine in England. PLoS ONE. 2016;11:e0149540. doi:10.1371/journal.pone.0149540.
7. Dirmesropian S, Wood JG, MacIntyre CR, Beutels P, McIntyre P, Menzies R, et al. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) in older Australians. Vaccine. 2017;35:4307–14. doi:10.1016/j.vaccine.2017.06.085.
8. Heo JY, Seo YB, Choi WS, Lee J, Noh JY, Jeong HW, et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLoS ONE. 2017;12:e0177342. doi:10.1371/journal.pone.0177342.
9. Chen C, Wood JG, Beutels P, Menzies R, MacIntyre CR, Dirmesropian S, et al. The role of timeliness in the cost-effectiveness of older adult vaccination: A case study of pneumococcal conjugate vaccine in Australia. Vaccine. 2018;36:1265–71. doi:10.1016/j.vaccine.2018.01.052.
10. Chen C, Beutels P, Newall AT. Evolution over time in the cost-effectiveness of pneumococcal conjugate vaccine (PCV13) in older Australians due to herd protection from infant vaccination. Vaccine. 2018;36:2057–60. doi:10.1016/j.vaccine.2018.03.006.
11. Thorrington D, van Rossum L, Knol M, Melker H de, Rümke H, Hak E, van Hoek AJ. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS ONE. 2018;13:e0192640. doi:10.1371/journal.pone.0192640.
12. Willem L, Blommaert A, Hanquet G, Thiry N, Bilcke J, Theeten H, et al. Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. Hum Vaccin Immunother. 2018:1–12. doi:10.1080/21645515.2018.1428507.
13. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30:6802–8. doi:10.1016/j.vaccine.2012.09.019.
14. Kuchenbecker U, Chase D, Reichert A, Schiffner-Rohe J, Atwood M. Estimating the cost-effectiveness of a sequential pneumococcal vaccination program for adults in Germany. PLoS ONE. 2018;13:e0197905. doi:10.1371/journal.pone.0197905.
15. Weycker D, Sato R, Strutton D, Edelsberg J, Atwood M, Jackson LA. Public health and economic impact of 13-valent pneumococcal conjugate vaccine in US adults aged ≥50 years. Vaccine. 2012;30:5437–44. doi:10.1016/j.vaccine.2012.05.076.
16. Smith KJ, Zimmerman RK, Lin CJ, Nowalk MP, Ko F-S, McEllistrem MC, Roberts MS. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine. 2008;26:1420–31. doi:10.1016/j.vaccine.2008.01.007.
17. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008:CD000422. doi:10.1002/14651858.CD000422.pub2.
18. Vila-Córcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodríguez T, Llor C. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis. 2006;43:860–8. doi:10.1086/507340.
19. Rodriguez-Barradas MC, Goulet J, Brown S, Goetz MB, Rimland D, Simberkoff MS, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. Clin Infect Dis. 2008;46:1093–100. doi:10.1086/529201.
20. Graf von der Schulenburg J-M, Greiner W, Jost F, Klusen N, Kubin M, Leidl R, et al. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. Value Health. 2008;11:539–44. doi:10.1111/j.1524-4733.2007.00301.x.
21. Knol MJ, Wagenvoort GHJ, Sanders EAM, Elberse K, Vlaminckx BJ, Melker HE de, van der Ende A. Invasive Pneumococcal Disease 3 Years after Introduction of 10-Valent Pneumococcal Conjugate Vaccine, the Netherlands. Emerging Infect Dis. 2015;21:2040–4. doi:10.3201/eid2111.140780.
22. Melegaro A, Edmunds WJ. Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. Vaccine. 2004;22:4203–14. doi:10.1016/j.vaccine.2004.05.003.
23. van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, Miller E. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65:17–24. doi:10.1016/j.jinf.2012.02.017.
24. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost Effectiveness in Health and Medicine. Pharmacoeconomics. 1997;11:159–68.
25. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2013. https://www.nice.org.uk/article/pmg9/. Accessed 18 Jun 2018.
26. Rozenbaum MH, van Hoek AJ, Fleming D, Trotter CL, Miller E, Edmunds WJ. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ. 2012;345:e6879. doi:10.1136/bmj.e6879.
27. Kothe H, Bauer T, Marre R, Suttorp N, Welte T, Dalhoff K. Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. Eur Respir J. 2008;32:139–46. doi:10.1183/09031936.00092507.
28. Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–25. doi:10.1056/NEJMoa1408544.
29. Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012;307:804–12. doi:10.1001/jama.2012.169.
30. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015;15:301–9. doi:10.1016/S1473-3099(14)71081-3.
31. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013:CD000422. doi:10.1002/14651858.CD000422.pub3.
32. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS ONE. 2017;12:e0169368. doi:10.1371/journal.pone.0169368.
33. Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325:1453–60. doi:10.1056/NEJM199111213252101.
34. Reinert RR, Haupts S, van der Linden M, Heeg C, Cil MY, Al-Lahham A, Fedson DS. Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001-2003. Clin Microbiol Infect. 2005;11:985–91. doi:10.1111/j.1469-0691.2005.01282.x.
35. Pletz MW, Ewig S, Rohde G, Schuette H, Rupp J, Welte T, et al. Impact of pneumococcal vaccination in children on serotype distribution in adult community-acquired pneumonia using the serotype-specific multiplex urinary antigen detection assay. Vaccine. 2016;34:2342–8. doi:10.1016/j.vaccine.2016.03.052.

S6. Conversion of ICER, costs and utilities extracted from the evaluated studies

S6 Table 1: Reported and converted ICER estimates for the studies selected for quality assessment of economic evaluation (n=13).

*** If the reference year was not reported, it was assumed that the reference year was two years before publication as this was the most common time period between reference year and publication year in the other studies.**

Scenario results in publication (Country/Publication year/reference year*)	ICER per	Model value	in 2017 $US
Jiang et al, 2012 (Germany/2010/Euro)			
basecase payer	QALY	17,065	$ 24,559
basecase societal	QALY	25,687	$ 36,967
Mangen et al, 2015 (The Netherlands/2012/Euro)			
Basecase	QALY	8,650	$ 12,003
95% CI lower	QALY	5,750	$ 7,979
95% CI upper	QALY	17,100	$ 23,729
basecase	LYG	7,650	$ 10,616
95% CI lower	LYG	5,300	$ 7,355
95% CI upper	LYG	12,450	$ 17,277
Blommaert et al, 2016 (Belgium/2014/Euro)			
PCV13 vs. No; 50-64 yoa	QALY	218,774	$ 287,917
PCV13 vs. No; 65-74 yoa	QALY	99,620	$ 131,104
PCV13 vs. No; ≥75 yoa	QALY	67,507	$ 88,842
PPSV23 vs. No; 50-64 yoa	QALY	128,859	$ 169,584
PPSV23 vs. No; 65-74 yoa	QALY	67,182	$ 88,415
PPSV23 vs. No; ≥75 yoa	QALY	49,760	$ 65,486
Gonzalez-Moro et al, 2016 (Spain/2015/Euro)			
basecase PCV13 vs current with PPSV23	QALY	1,844	$ 2,992
50–64 years, PCV13 vs current with PPSV23	QALY	9,800	$ 15,901
65–74 years, PCV13 vs current with PPSV23	QALY	3,475	$ 5,638
basecase,PCV13 vs current with PPSV23	LYG	1,245	$ 2,020
Stoecker et al, 2016 (USA/2013/US-$)			
add PCV13 at 50 yoa; basecase	QALY	333,200	$ 365,482
add PCV13 at 50 yoa; 95% CI lower	QALY	159,370	$ 174,810
add PCV13 at 50 yoa; 95% CI upper	QALY	431,171	$ 472,944
add PCV13 at 60 yoa; basecase	QALY	238,227	$ 261,307
add PCV13 at 60 yoa; 95% CI lower	QALY	131,641	$ 144,395
add PCV13 at 60 yoa; 95% CI upper	QALY	355,424	$ 389,859
add PCV13 at 65 yoa; basecase	QALY	62,065	$ 68,078
add PCV13 at 65 yoa; 95% CI lower	QALY	26,951	$ 29,562
add PCV13 at 65 yoa; 95% CI upper	QALY	147,828	$ 162,150
replace PPSV23 at 65 yoa; basecase	QALY	46,396	$ 50,891
van Hoek et al, 2016 (England/2014/GBP)			
Basecase	QALY	257,771	$ 375,622
Dirmesropian et al, 2017 (Australia/2016/AUS-$)			
PCV13 vs. No; basecase	QALY	88,000	$ 62,417
PPSV23 vs. No; basecase	QALY	297,200	$ 210,800
PCV13 vs PPSV23	QALY	35,300	$ 25,038
Heo et al, 2017 (Korea/NA/US-$)			
60% coverage >65y.o. with PCV13; basecase vs Current	QALY	797	$ 1,099
80% coverage; >65y.o. with PCV13; basecase vs Current	QALY	701	$ 967
60% coverage >65y.o. with PPSV23; vs No	QALY	25,786	$ 35,565
80% coverage >65y.o. with PPSV23; vs No	QALY	17,354	$ 23,936
60% coverage >65y.o. with PCV13; vs No	QALY	4,529	$ 6,247

80% coverage >65y.o. with PCV13; vs No	QALY	5,045	$	6,958
Sequential PCV13-PPSV23, 60% vs Curr	QALY	1,228	$	1,694
Sequential PCV13-PPSV23, 80% vs Curr	QALY	10,645	$	14,682
Chen et al, 2018 (Australia/2016/AUS-$)				
recommended age; basecase vs No	QALY	83,538	$	59,252
observed age; basecase vs No	QALY	65,269	$	46,294
Chen et al, 2018 (Australia/2016/AUS-$)				
basecase	QALY	71,000	$	50,359
serotype evolution	QALY	171,000	$	121,288
Thorrington et al, 2018 (The Netherlands/NA/Euro)				
basecase	QALY	6,201	$	7,925
Willem et al, 2018 (Belgium/2015/Euro)				
PCV13 in 50-64 y.o. vs current PPSV23 low uptake	QALY	201,172	$	260,611
PPSV23 in 50-64 y.o. vs current PPSV23 low uptake	QALY	82,814	$	107,282
PCV13+PPSV23 in 50-64 y.o. vs current PPSV23 low uptake	QALY	168,879	$	218,776
PCV13 in 65-74y.o. vs current PPSV23 low uptake	QALY	171,344	$	221,970
PPSV23 in 65-74y.o. vs current PPSV23 low uptake	QALY	57,212	$	74,116
PCV13+PPSV23 in 65-74 y.o. vs current PPSV23 low uptake	QALY	132,590	$	171,765
PCV13 in 75-84y.o. vs current PPSV23 low uptake	QALY	338,159	$	438,072
PPSV23 in 75-84y.o. vs current PPSV23 low uptake	QALY	52,147	$	67,554
PCV13+PPSV23 in 75-84 y.o. vs current PPSV23 low uptake	QALY	155,395	$	201,308
Kuchenbecker et al, 2018 (Germany/NA/Euro)				
LR and MR initial vaccination with PCV13, high risk , sequential, payer	LYG	3,662	$	4,794
LR and MR initial vaccination with PCV13, high risk , sequential, payer	QALY	5,828	$	7,630
LR and MR initial vaccination with PCV13, high risk , sequential, societal	LYG	3,258	$	4,265
LR and MR initial vaccination with PCV13, high risk , sequential, societal	QALY	5,186	$	6,789
Sequential for all risk groups PCV13+PPSV23, payer	LYG	8,964		
Sequential for all risk groups PCV13+PPSV23, payer	QALY	14,881	$	19,482
Sequential for all risk groups PCV13+PPSV23, societal	LYG	8,447	$	11,059
Sequential for all risk groups PCV13+PPSV23, societal	QALY	14,023	$	18,358
LR according to STIKO, sequential only for MR and HR , payer	LYG	7,013	$	9,181
LR according to STIKO, sequential only for MR and HR , payer	QALY	11,584	$	15,165
LR according to STIKO, sequential only for MR and HR , societal	LYG	6,459	$	8,456
LR according to STIKO, sequential only for MR and HR , societal	QALY	10,667	$	13,965

S6 Table 2: Reported and converted cost estimates (n=13)

Cost component in publication (Country/Publication Year/Reference Year/Model currency)	Perspective	Model value	in 2017 US-$
Jiang et al. 2012 (Germany/2010/Euro)			
PPSV23 vaccine	TTP	30,25 €	$44,94
Adminstration	TTP	6,95 €	$10,33
Meningitis	TTP	11.664,00 €	$17.329,46
Invasive pneumonia	TTP	8.075,00 €	$11.997,20
NBPP inpatient	TTP	5.762,00 €	$8.560,73
NBPP outpatient	TTP	78,00 €	$115,89
Meningitis Sequelae Hearing Loss (per year)	TTP	1.552,00 €	$2.305,84
Meningitis Sequelae Neurological (per year)	TTP	862,00 €	$1.280,69
PPSV23 vaccine	societal	38,25 €	$56,83
Adminstration	societal	13,95 €	$20,73
Meningitis	societal	11.671,00 €	$17.339,86
Invasive pneumonia	societal	8.082,00 €	$12.007,60
NBPP inpatient	societal	5.769,00 €	$8.571,13
NBPP outpatient	societal	85,00 €	$126,29
Meningitis Sequelae Hearing Loss	societal	1.559,00 €	$2.316,24
Meningitis Sequelae Neurological	societal	869,00 €	$1.291,09
Productivity loss IPD	societal	1.612,80 €	$2.396,17
Productivity loss NBPP	societal	1.612,80 €	$2.396,17
Productivity loss PMS	societal	35.064,00 €	$52.095,34
Mangen et al, 2015 (The Netherlands/2012/Euro)			
Vaccine costs	societal	79,19 €	$107,84
DHC IPD	societal	Age-, risk-group and outcome dependent	
DHC inpatient CAP	societal	Age-, risk-group and outcome dependent	
DHC outpatient CAP	societal	78,25 €	$106,56
DNHC IPD fatal case	societal	11,90 €	$16,20
DNHC IPD survivor	societal	27,70 €	$37,72
DNHC inpatient CAP fatal case	societal	11,90 €	$16,20
DNHC inpatient CAP survivor	societal	27,70 €	$37,72
DNHC outpatient CAP	societal	20,26 €	$27,59
INHC IPD	societal	Age-, risk-group and outcome dependent	
INHC inpatient CAP	societal	Age-, risk-group and outcome dependent	
INHC outpatient CAP	societal	453,01 €	$616,88
Blommaert et al, 2016 (Belgium/2014/Euro)			
Vaccine price PCV13	TTP	74,55 €	$99,85
Vaccine price PPSV23	TTP	28,46 €	$38,12
Vaccine administration	TTP	23,32 €	$31,23
Cost of hearing aids (every 7 years)	TTP	1.000,00 €	$1.339,40
Cost of long-term sequelae	TTP	35.000,00 €	$46.878,97
DHC outpatient pneumonia	TTP	1.032,00 €	$1.382,26
DHC inpatient pneumonia (50 yoa)	TTP	9.118,00 €	$12.212,64
DHC inpatient meningitis (50 yoa)	TTP	9.415,00 €	$12.610,44
DHC inpatient septicemia (50 yoa)	TTP	7.365,00 €	$9.864,67
DHC inpatient pneumonia (65 yoa)	TTP	11.476,00 €	$15.370,94
DHC inpatient meningitis (65 yoa)	TTP	9.925,00 €	$13.293,54
DHC inpatient septicemia (65 yoa)	TTP	10.961,00 €	$14.681,15
DHC inpatient pneumonia (75 yoa)	TTP	12.096,00 €	$16.201,37
DHC inpatient meningitis (75 yoa)	TTP	10.254,00 €	$13.734,20
DHC inpatient septicemia (75 yoa)	TTP	12.673,00 €	$16.974,21
DHC inpatient pneumonia (90 yoa)	TTP	14.267,00 €	$19.109,21

DHC inpatient meningitis (90 yoa)	TTP	10.909,00 €	$14.611,51
DHC inpatient septicemia (90 yoa)	TTP	14.940,00 €	$20.010,62
Stoecker et al, 2016 (USA/2013/US-$)			
Vaccine	societal	$85,19	$97,15
Vaccine administration	societal	$40,00	$45,61
DHC IPD 50-64 healthy	societal	$40.161,00	$45.797,47
DHC IPD 50-64 high risk	societal	$40.161,00	$45.797,47
DHC IPD >65 healthy	societal	$27.097,00	$30.899,98
DHC IPD >65 high risk	societal	$27.097,00	$30.899,98
DHC inpatient NBP 50-64 healthy	societal	$34.948,00	$39.852,84
DHC inpatient NBP 50-64 high risk	societal	$34.948,00	$39.852,84
DHC inpatient NBP >65 healthy	societal	$23.296,00	$26.565,52
DHC inpatient NBP >65 high risk	societal	$23.296,00	$26.565,52
DHC outpatient NBP 50-64 healthy	societal	$127,00	$144,82
DHC outpatient NBP 50-64 high risk	societal	$127,00	$144,82
DHC outpatient NBP >65 healthy	societal	$254,00	$289,65
DHC outpatient NBP >65 high risk	societal	$254,00	$289,65
van Hoek et al, 2016 (England/2014/GBP)			
Vaccine	TTP	£49,10	$72,56
Vaccine administration	TTP	£7,51	$11,10
Hospitalization IPD (65 yoa)	TTP	£4.865,00	$7.189,48
Hospitalization IPD (100 yoa)	TTP	£4.780,00	$7.063,87
Hospitalization CAP	TTP	£715,00	$1.056,62
Dirmesropian et al, 2017 (Australia/2016/AUS-$)			
Vaccine costs PPSV23	TTP	$35,00	$25,22
Vaccine costs PCV13	TTP	$65,00	$46,83
Vaccine administration	TTP	$10,00	$7,20
DHC outpatient CAP	TTP	$114,00	$82,13
Meningitis hospitalisation (≥65)	TTP	$35.499,00	$25.575,64
Bacteraemia (all non-meningitis) hospitalisation (65-69)	TTP	$18.610,00	$13.407,78
Bacteraemia (all non-meningitis) hospitalisation (70-74)	TTP	$18.695,00	$13.469,01
Bacteraemia (all non-meningitis) hospitalisation (75-79)	TTP	$16.803,00	$12.105,90
Bacteraemia (all non-meningitis) hospitalisation (80-84)	TTP	$18.023,00	$12.984,87
Bacteraemia (all non-meningitis) hospitalisation (≥85)	TTP	$15.036,00	$10.832,85
Non-invasive CAP hospitalisation (65-69)	TTP	$8.140,00	$5.864,55
Non-invasive CAP hospitalisation (70-74)	TTP	$8.316,00	$5.991,35
Non-invasive CAP hospitalisation (75-79)	TTP	$8.387,00	$6.042,50
Non-invasive CAP hospitalisation (80-84)	TTP	$8.429,00	$6.072,76
Non-invasive CAP hospitalisation (≥85)	TTP	$8.340,00	$6.008,64
Chen et al. 2018a & 2018b (Australia/2016/AUS-$)			
Vaccination cost PCV13	TTP	$65,00	$46,83
Vaccine administration	TTP	$10,00	$7,20
DHC outpatient CAP	TTP	$126,00	$90,78
DHC inpatient Meningitis (50-64 yoa)	TTP	$31.178,00	$22.462,53
DHC inpatient Meningitis (>= 65 yoa)	TTP	$37.848,00	$27.268,00
DHC inpatient Non-Meningitis IPD (50-64 yoa)	TTP	$29.609,00	$21.332,12
DHC inpatient Non-Meningitis IPD (65-69 yoa)	TTP	$19.650,00	$14.157,05
DHC inpatient Non-Meningitis IPD (70-74 yoa)	TTP	$19.740,00	$14.221,90
DHC inpatient Non-Meningitis IPD (75-79 yoa)	TTP	$17.743,00	$12.783,14
DHC inpatient Non-Meningitis IPD (80-84 yoa)	TTP	$19.031,00	$13.711,09
DHC inpatient Non-Meningitis IPD (≥85 yoa)	TTP	$15.877,00	$11.438,76
DHC inpatient CAP (50-64 yoa)	TTP	$7.899,00	$5.690,92

DHC inpatient CAP (65-69 yoa)	TTP	$8.595,00	$6.192,36
DHC inpatient CAP (70-74 yoa)	TTP	$8.781,00	$6.326,37
DHC inpatient CAP (75-79 yoa)	TTP	$8.856,00	$6.380,40
DHC inpatient CAP (80-84 yoa)	TTP	$8.900,00	$6.412,10
DHC inpatient CAP (≥85 yoa)	TTP	$8.806,00	$6.344,38
Thorrington et al, 2018 (The Netherlands/NA/Euro)			
Vaccine cost PCV13	TTP	72,67 €	$95,12
Vaccine cost PPSV23	TTP	21,20 €	$27,75
Vaccine cost PCV10	TTP	60,56 €	$79,27
DHC IPD	TTP	14.584,00 €	$19.089,08
DHC CAP	TTP	7.872,00 €	$10.303,71
Willem et al. 2018 (Belgium/2015/Euro)			
Vaccine costs PPSV23	TTP	28,46 €	$37,15
Vaccine costs PCV13	TTP	74,55 €	$97,31
Vaccine administration	TTP	11,70 €	$15,27
DHC inpatient Meningitis 50-64 yoa	TTP	7.686,00 €	$10.032,95
DHC inpatient Meningitis 65-74 yoa	TTP	8.900,00 €	$11.617,65
DHC inpatient Meningitis 75-84 yoa	TTP	9.103,00 €	$11.882,63
DHC inpatient Meningitis ≥85 yoa	TTP	6.973,00 €	$9.102,23
DHC inpatient Septicemia 50-64 yoa	TTP	8.114,00 €	$10.591,64
DHC inpatient Septicemia 65-74 yoa	TTP	6.317,00 €	$8.245,92
DHC inpatient Septicemia 75-84 yoa	TTP	5.003,00 €	$6.530,68
DHC inpatient Septicemia ≥85 yoa	TTP	3.137,00 €	$4.094,89
DHC inpatient Pneumonia 50-64 yoa	TTP	5.669,00 €	$7.400,05
DHC inpatient Pneumonia 65-74 yoa	TTP	5.909,00 €	$7.713,33
DHC inpatient Pneumonia 75-84 yoa	TTP	1.679,00 €	$2.191,69
DHC inpatient Pneumonia ≥85 yoa	TTP	3.466,00 €	$4.524,36
DHC outpatient pneumonia	TTP	80,90 €	$105,60
hearing loss 1st year	TTP	11.619,00 €	$15.166,90
hearing loss following years	TTP	1.498,00 €	$1.955,42
neurological	TTP	35.000,00 €	$45.687,38

S6 Table 3: Reported utilities (n=13)

Study	Parameter	Value
Jiang et al. 2012	IPD utility	0.2
	IPD duration	0.09315068
	IPD QALY loss	0.01863014
	NBPP utility	0
	NBPP duration	NA
	NBPP QALY loss	0
	PMS Hearing Loss utility	0.8
	PMS neurological utility	0.6
Mangen et al. 2015	QALY loss IPD	0.0709
	QALY loss inpatient CAP	0.0709
	QALY loss outpatient CAP	0.0045
Blommaert et al. 2016	QALY loss inpatient pneumonia	0.006
	QALY loss outpatient pneumonia	0.004
	QALY loss Meningitis	0.46
	QALY loss Septicemia	0.0079
Stoecker et al. 2016	QALY loss inpatient NBP	0.006
	QALY loss outpatient NBP	0.004
	QALY loss IPD	0.009
van Hoek and Miller 2016	QALY loss IPD (65 yoa)	0.14
	QALY loss IPD (100 yoa)	0.01
	QALY loss CAP	0.006
Dirmesropian et al. 2017	IPD (acute phase) hospitalisation	0.0709
	Non-invasive CAP (acute phase)	0.0709
	General practitioner visit	0.0045
Chen et al. 2018a & 2018b	QALY loss IPD inpatient	0.0709
	QALY loss CAP inpatient	0.0709
	QALY loss CAP outpatient	0.0045
Thorrington et al. 2018	QALY loss IPD	0.0709
	QALY loss CAP	0.0709
Willem et al. 2018	QALY loss IPD <65 yoa	0.0491
	QALY loss non-IPP <65 yoa	0.0203
	QALY loss IPD ≥65 yoa	0.0679
	QALY loss non-IPP ≥65 yoa	0.1741
	QALY loss outpatient pneumonia	0.0118
	Utility weight hearing loss	0.635
	Utility weight neurological	0.319