ROBERT KOCH INSTITUT

Version 1.0 (last updated: 16 March 2016)

Modelling methods for predicting epidemiological and health economic effects of vaccinations

Guidance for analyses to be presented to the German Standing Committee on Vaccination (STIKO)

Citation:

STIKO (2016) Modelling methods for predicting epidemiological and health economic effects of vaccinations – Guidance for analyses to be presented to the German Standing Committee on Vaccination (STIKO) (last updated: 16 March 2016), Berlin

Preamble

In Germany, the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute (RKI) develops and endorses recommendations for vaccinations in accordance with § 20 of the Prevention and Control of Infectious Diseases Act (in German: Infektionsschutzgesetz, IfSG). One of the primary tasks of STIKO is to develop an immunization schedule for infants, children, and adults. The committee is responsible for defining which vaccinations the general population or specific subpopulations (risk groups) should receive, when they should receive them, and at what intervals. In accordance with the aims of the IfSG, those vaccinations that have significant impact on public health are of particular relevance [1].

The STIKO is an independent panel of experts whose work is coordinated by and receives scientific support from its executive secretariat at RKI. The STIKO was installed in 1972 and was legally embedded in the IfSG in 2001. Since the Act on Competition Reinforcement in Statutory Health Insurance entered into force in 2007, vaccinations recommended by STIKO are the basis for the Vaccination Directive issued by the Federal Joint Committee (G-BA). Statutory health insurances in Germany are required to offer the vaccinations listed in this directive as a standard benefit [2].

Based on its rules of procedure, the STIKO defines its methodology according to the current state of the art. In developing its vaccination recommendations, STIKO follows the systematic methods of evidence-based medicine (EbM) [3]. In 2011, an updated methodology was established and summarized in a standard operating procedure (SOP) document that is updated as needed[1]. When developing a vaccination recommendation, the STIKO conducts an epidemiological-medical risk-benefit analysis. This analysis considers both, the individual benefits to a vaccinated person and the benefit of vaccination at population level which might include for example herd protection effects. Adverse effects of a vaccination strategy can also arise at population level (e.g. replacement phenomena, age shift of the disease burden). These effects have to be taken into account when developing a vaccination recommendation. The SOP also mentions the consideration of results from epidemiological-mathematical models (EM) and/or health economic evaluations (HE) for decision making. EMs and HEs aim to project the future epidemiological and economic impact of a (new) vaccination recommendation or strategy in a population. Most vaccination committees in Europe routinely apply EMs and HEs – besides other key criteria – as an important evidence basis for their vaccination recommendations [4].

This methods paper describes how mathematical models for predicting the epidemiological and health economic effects of vaccination should be performed to be presented to STIKO. This methods paper shall be routinely reviewed and updated as necessary. The target audience of this methods paper is the professional community.

[1] Standard operating procedure (SOP) of the German Standing Committee on Vaccinations (STIKO) http://www.rki.de/EN/Content/infections/Vaccination/methodology/SOP.pdf?__blob=publicationFile

This methods paper was developed within a research project funded by the Federal Ministry of Health (BMG) (www.rki.de/steering). It aims to make a further contribution to the standardization of the STIKO workflow, the quality of vaccination recommendations in Germany, and the transparency of the decision making processes. This methods paper will describe the EM approach of predicting epidemiological effects and HEs. The manner in which analyses of certain vaccinations should be designed depends, among other things, on the respective research question and the scientific evidence available. For that reason, its presentation is project-specific.

EMs and HEs commissioned by STIKO or the RKI are primarily intended to support the STIKO in developing the most efficient vaccination strategy. However, the results of EMs and HEs are only one aspect upon which the STIKO bases its decisions.

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Abbreviations

BMG	The Federal Ministry of Health (in German: Bundesministerium für Gesundheit)
e.g.	For example
DSA	Deterministic sensitivity analysis
EbM	Evidence-based medicine
EM	Epidemiological-mathematical model
EntgFZG	Continued Remuneration Act (covering sick and holiday pay, in German: Gesetz über die Zahlung des Arbeitsentgelts an Feiertagen und im Krankheitsfall)
G-BA	The Federal Joint Committee (in German: Gemeinsamer Bundesausschuss)
HE	Health economic evaluation
SHI	Statutory health insurance
ICER	Incremental cost-effectiveness ratio
IfSG	Prevention and Control of Infectious Diseases Act (in German: Infektions schutzgesetz)
IQWiG	Institute for Quality and Efficiency in Health Care (German: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ITT	Intention to treat
NNV	Number needed to vaccinate
PP	Per protocol
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RKI	Robert Koch Institute
SGB V	The German Social Code, Book Five (in German: Sozialgesetzbuch Fünftes Buch)
SI-RL	Vaccination Directive (in German: Schutzimpfungsrichtlinie)
SOP	Standard operating procedure
STIKO	Standing Vaccination Committee (in German: Ständige Impfkommission)
WHO	World Health Organization
WSG	Competition Reinforcement Act (in German: Wettbewerbsstärkungsgesetz)

1 Methods of epidemiological-mathematical modelling and health economic evaluations

1.1 Introduction

In Germany there are currently two methods papers that describe the technical framework for conducting health economic evaluations (HEs): the 'General Methods' of the Institute for Quality and Efficiency in Health Care (IQWiG), and the 'Hannover Consensus' [5, 6]. These papers primarily target the evaluation of pharmaceuticals, and less primary preventive measures such as vaccinations against infectious diseases [7] (p. 255)[2]. However, the approaches and methods are at least partially different for conducting epidemiological-mathematical models (EMs) and HEs of vaccinations [8-10].

The Robert Koch Institute (RKI) cooperated with national and international experts to identify the particularities that should be taken into account when conducting EMs and HEs for vaccinations. Section 1 of this methods paper is based on chapter 4 of the IQWiG 'General Methods', the 'Hannover Consensus', on comprehensive literature research as well as consensuses developed with these experts [5, 6]. Here, aspects are addressed that are in particular relevant for EMs and HEs of vaccinations. Aspects that are not explicitly or only briefly addressed here are usually explained in more detail in the publications named above; this does, however, not constitute an endorsement of the approaches in those methods papers [5, 6, 11].

When conducting an EM or HE, the target population, e.g. the population of a country, is first patterned according to its demographic attributes in order to apply the target diseases addressed by the specific research question and extrapolate their distribution in this target population for a certain period of time [10]. In a next step, the relevant vaccination is implemented in the model and applied to the same population, depending on design and vaccination strategy. Then the impact of the particular vaccination strategy on the disease distribution is analysed. The initial aim is to calculate and compare the aspects relevant to public health: the number of (prevented) medical-epidemiological outcomes, for example illnesses, hospitalizations, and/or deaths with and without implemented vaccination, as well as the adverse effects caused by the vaccination at population level. In an HE, the corresponding direct and indirect costs of treating the target disease and the costs of the vaccination are added to these public health aspects in order to calculate health economic figures, such as the incremental cost-effectiveness ratio (ICER). Because of the large quantity of data needed, such models only generate valid findings if sufficiently valid input data are available or if the model can be calibrated based on extensive data on disease burden. The availability of data should be determined before conducting any modelling project. Any limitations occurring (due to data availability) should be clearly documented, assessed, and critically discussed during the modelling, in particular if data from other countries have been used.

[2] According to SGB V, section 139a, paragraph 3, number 2, the IQWiG can be commissioned with assessments of quality and efficiency of other services provided by statutory health insurance.

In principle, models that STIKO potentially considers for its decision making, as described in section 1, can be performed by external institutions. Due to the generally high level of complexity, the high level of coordination required, and the frequent risk of intransparency, STIKO prefers commissioning its own models with close monitoring and frequent updates. The STIKO or the relevant STIKO workgroup will work with STIKO's executive secretariat and RKI's Immunization Unit to define all project-specific modelling requirements, and involve other experts or project partners as needed.

Section 1.2 focuses primarily on EM and its particularities regarding vaccinations. Section 1.3 addresses the special health economic requirements that should be taken into account in an HE on vaccinations. Remarks on the following sections have also been made in other places and illustrated using examples [11].

1.2 Epidemiological modelling

1.2.1 Selecting a model type

Numerous studies on the various types of models and the selection of a model can be found in the literature [8, 12-28]. There are various types of models: (i) cohort models, (ii) population models, and (iii) individual-based models. Category (i) models are static, for example decision trees or Markov models. They are not able to represent the transmission of pathogens between individuals or segments of populations. Category (ii) and (iii) models, on the other hand, can depict these transmissions and thus reproduce the spread of infectious diseases. They are called dynamic models. Category (i) and (ii) models are often deterministic in nature, whereas category (iii) models are stochastic [11].

In general, dynamic models should be used if vaccinations or vaccination strategies can lead to indirect effects (e.g. herd protection) in the population. The use of static models is legitimate for the evaluation of vaccinations and vaccination strategies that do *not* lead to indirect effects (e.g. tetanus vaccinations). The World Health Organization (WHO) flow chart is of assistance here [29], see illustration 1. In certain circumstances a static model can also be used to evaluate vaccinations/vaccination strategies that can lead to indirect effects. For example, one condition could be that a static model represents a conservative approach in which indirect positive effects, e.g. herd protection, are not taken into account. But that is appropriate only if it does not lead to any negative indirect effects, e.g. serotype replacement or age shifting of the incidence with a corresponding rise in the probability of complications, being neglected [20, 22, 29-31]. When using a dynamic model, in particular a model with a long time horizon, it should be considered beforehand whether realistic demographic projections for Germany [32] (e.g. demographic change, migration, or contact patterns in the population) should be utilized, or whether a stable population should be assumed in the model. In this situation, uncertainty analyses that are particularly comprehensive are needed [11, 33].

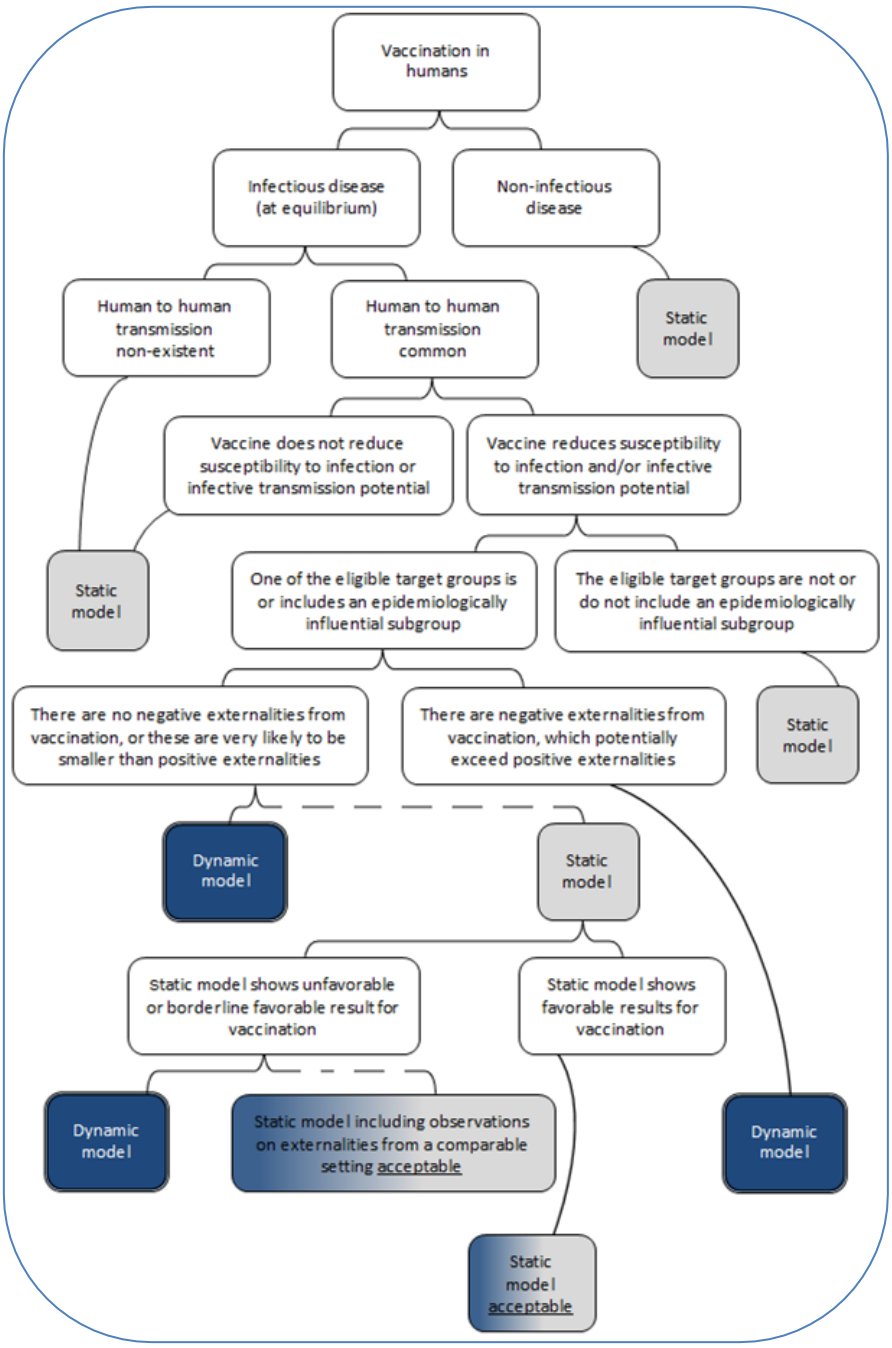

Figure 1 WHO flow chart for selecting models [29]

1.2.2 Documentation of a model

Transparent, detailed, and reproducible documentation of a model is essential in both, model code (regardless of software[3]) and written report.

[3] For example 'R', a free programming language for statistical calculations (https://www.r-project.org/)

1.2.3 Time horizon of dynamic models

The time horizon of static models usually corresponds to the duration of the age segment at highest risk of acquiring the disease analysed, or the lifetime of the cohort(s) observed in the model. The time horizon of a dynamic model is somewhat more complex, and has an enormous impact of the validity and results of the model [13, 18, 23]. This time horizon can usually be subdivided into three consecutive phases:

(i) Run-in phase (also called burn-in phase): Dynamic models require a run-in phase in order to reproduce the epidemiological situations in the pre-vaccination periode. This is important for the realistic implementation of respective vaccination. The length of this phase can influence the results of the model.

(ii) Evaluation phase: This phase starts with the implementation of the vaccination in the target population. The length of the evaluation phase should be set so that both positive and negative effects of the vaccination can be depicted and taken into account.

(iii) Steady-state: After a certain period of time in the evaluation phase, an epidemiological plateau, called the steady-state, is reached. This is where the epidemiological variations terminate. The time horizon of a model should extend to this steady-state so that valid and dependable results can be generated.

The time horizon of the evaluation should be described and justified. In addition to the ICERs calculated from the steady-state phase, ICERs varying points of time before the steady-state should be calculated and presented [11, 22].

1.2.4 Comparators

Depending on the research question, there are various ways to conduct comparisons, e.g. no-vaccination vs. vaccination, a screening program vs. vaccination, or an existing vaccination strategy vs. a new vaccination strategy for the same disease (e.g. changing the age at vaccination, vaccinating boys and girls, vaccinating girls only). All health care-relevant preventive or curative comparators in the therapeutic indication of the respective vaccination should be included in the model. If they are not included, the reasons for this should be given.

1.2.5 Endpoints

Modelling should take all endpoints relevant to the respective indication into account (e.g. disease case, complications, hospitalization and/or death), as well as the measure of benefit in the form of quality-adjusted life years (QALYs) [34].

1.2.6 Natural disease progression

The structure of a model correlates directly to and should be developed based on the natural progression of the disease for which a vaccine is administered [20, 35]. Examples of structures for compartment models (cf. category (ii) in section 1.2.1) include ‘susceptible-infectious-susceptible’

(SIS), 'susceptible-infectious-recovered' (SIR), 'susceptible-infectious-recovered-susceptible' (SIRS), and 'susceptible-exposed-infectious-recovered-susceptible' (SEIRS). In general the model structure should be developed based on the characteristics of the respective disease, the vaccine/vaccination, and the research question. In dynamic models, the pathogen-specific naturally acquired immunity (after infection) and the waning of this immunity over time are particularly important. If there are any uncertainties regarding the natural disease progression and thus the model structure, the structure should be varied in uncertainty analyses [36, 37].

1.2.7 Measures of vaccine-induced protection

There are various approaches for defining vaccine-induced protection and thus vaccine efficacy within models [24, 28, 38-40]. A vaccine can protect from infection, symptomatic illness, complications and/or infectiousness. The vaccine-induced protection should be modelled according to the respective disease and the vaccine available. In some cases a hierarchy of various endpoints should also be incorporated in the model. One type of hierarchy is a sequential hierarchy. In a sequential hierarchy, vaccine-induced protection is applied only to the primary endpoint, and all others are disregarded in modelling the vaccine-induced protection. Vaccine-induced protection can also be applied to all relevant endpoints, depending on the vaccine and the study findings. The structure of a model and the approach to modelling the vaccine-induced protection should be designed in accordance with medical evidence. Whether a vaccine reduces infectiousness or susceptibility to infection in a model is a key difference that has an enormous impact on the model results. Uncertainties and their impact on the findings of vaccine-induced protection models should be considered in uncertainty analyses.

In clinical trials there are two approaches of analysis to usually measure vaccine efficacy (VE). These include the *per protocol (PP)* and *intention to treat (ITT)* variants [41]. PP normally generates results that favour vaccination/intervention, whereas ITT procedures normally produce rather conservative results. Whenever ITT efficacy data are available for a new vaccine, these should be used in a model's base case. PP data can be used in uncertainty analyses. PP data can also be used in the base case if the difference between ITT and PP can be fully explained by the differing proportions of persons susceptible in the study populations.

To some extent in clinical market authorization studies of vaccines, efficacy is not measured based on clinical endpoints, but instead using surrogate parameters such as immunogenicity. But the link between immunogenicity and actual vaccine-induced protection is not always clear. Only validated surrogates (e.g. proof of correlation of the effects on the surrogate to the effect on the patient-relevant endpoint) should be considered as endpoints, and uncertainty analyses should be conducted.

Models should also describe and distinguish between vaccine-induced protection through *degree of protection* or *take*. The degree of protection is the vaccine-induced protection in individuals who are completely vaccinated (e.g. 100% of the individuals completely vaccinated have 50% protection).

Take is the percentage of completely vaccinated individuals with full protection (e.g. 50% of the completely vaccinated individuals have 100% protection) [42]. The respective vaccine will determine which approach should be used in the model. If there is no evidence for this, uncertainty analyses should be conducted. Adverse effects of vaccinations at the individual level (adverse drug reactions) and population level (e.g. replacement effects) should also be taken into account in model and, if applicable, in uncertainty analyses.

1.2.8 Duration of vaccine-induced protection

The duration of vaccine-induced protection has a major impact on model results; waning of this protection is crucial [20, 35]. Often there are no reliable data on vaccine-related waning at the time of market authorization because the duration of most clinical trials is too short to adequately reflect the duration of vaccine-induced protection and its waning. That means that assumptions must be made in models. If necessary, it is possible to assume lifelong protection or waning. Waning (e.g. exponential or stepwise) can start immediately after vaccination or after a period of stability (vaccine-induced protection remains constant at first). If there are uncertainties about this, comprehensive uncertainty analyses should be conducted.

1.2.9 Indirect effects of vaccination

Beyond the positive indirect effect of vaccine-induced herd protection, there are also negative indirect effects (such as age shifting of incidence accompanied by a rising probability of complications or serotype replacement) caused by vaccination or a vaccination strategy. If relevant, these should be regarded in models [13, 14, 18, 20, 23]. In addition, consequences such as intrapopulation effects, for instance the impact of the vaccination of children on the disease burden of the elderly (e.g. varicella zoster virus or pneumococci) or antibiotic resistance, should be reflected in models if relevant. Potential consequences of vaccination, such as eradication of the pathogen or behavioural changes (e.g. risk behaviour, screening) can also play an important role and should be analysed in models if relevant.

1.2.10 Vaccination target group

Beyond the question of who should be vaccinated (e.g. the entire population or certain risk groups), the question of contact patterns in the target group is of particular importance and should be depicted adequately in dynamic models [14, 16, 20, 24, 39, 43]. There are various data collection methods for contact patterns, such as questionnaires (e.g. POLYMOD [44]) or synthetic contact patterns based on demographic data [45, 46]. In Germany, methods based on questionnaires should be used whenever possible.

1.2.11 Model calibration and validation

Model calibration is an instrument that is already used during model development [47]. For the valid modelling of future effects, a model should be able to reproduce disease progression and spread retrospectively (if applicable without intervention/vaccination, see section1.2.3 ‘run-in

phase'). Often, however, the input data available for the model parameters are insufficient, with the result that past incidence progression is nearly impossible to reproduce. Model calibration, also called estimation of model parameters, is the procedure of mathematical model adjustment in which model parameters are set in a manner that model results fit well to observations in reality [13, 16, 22, 24, 36, 48-52]. There are different calibration methods, for example manual, random (e.g. Monte Carlo), and optimizing (e.g.: Nelder-Mead [53]) methods. The calibration process should always be conducted in a transparent and well-structured way; for that reason random or optimizing methods should preferably be applied [48, 51, 54, 55]. Careful attention should also be paid to whether the model parameters estimated by calibration are plausible.

Besides calibration and transparency, validation is the instrument that can increase the credibility of the generated model results [48, 54]. There are several different types of validation [54]. In plain visual validation, the operation mode of the model including its assumptions is examined for quality and plausibility by experienced experts. The verification process examines whether the model (mathematically) processes and calculates the data correctly. External validation compares model results with the best available evidence in order to examine the plausibility of the calculations. However, in a validation process, a purely visual validation is not sufficient. Instead, *goodness-of-fit* criteria should be taken into account (e.g. adjustment tests for the predictive distribution of the data according to the model [56]). It is important that the same data set (including endpoints) is not used for calibration and validation. Alternatively, a fraction of the data can be used for validation instead of calibration, or *cross-model validation* can be conducted [57]. In cross-model validation, various models that have been developed for the same research question are compared to one another. The same data set is used in the various models.

1.2.12 Dealing with uncertainty

In literature, various types of uncertainty and approaches for handling them in these models can be found [13, 15, 20, 22-24, 28, 40, 58, 59] (table 1). Structural (model) uncertainty should be analysed using either scenario analyses (e.g. results from various models/model structures) or, preferably, by parametrisation of the structural uncertainty [60-62]. Parameter uncertainty should be illustrated with probabilistic sensitivity analyses (PSA). However, PSAs are often a challenge for dynamic models since parameters that enable transmission often do not generate plausible results. Alternatives can be not including these transmission parameters in the PSA, or developing two models: a dynamic model that represents epidemiology and transmission, and a static (sub-)model that also includes a PSA. Uncertainty analyses (PSAs or other analyses) should always be conducted for all sources of uncertainty, in particular for vaccination-specific input parameters. For example the duration of vaccine-induced protection, the vaccination coverage, the model's time horizon, the utilisation of vaccination boosters, contact patterns, and target groups should be analysed. In a PSA, the determination of the probability distributions upon which each parameter is based should be justified and explained. If possible, calibrated parameters should be analysed in uncertainty analyses as well [37, 63]. Normative variables, for example the selection of perspective (SHI or societal

perspective), the vaccine price, vaccination administration honoraria, or the discount should not to be included in PSA [37, 63]. Nevertheless, several PSAs, e.g. with a different set of discount rates or vaccine prices, should be conducted to illustrate the *methodological/normative* uncertainty [64]. The vaccination coverage should be varied between desired and undesired levels.

	Sensitivity analyses			Scenario analyses
Type of uncertainty	Parameter uncertainty	Methodological/ normative uncertainty	Structural/ model uncertainty	
Deterministic sensitivity analysis (DSA)	Yes	Yes	Yes	Yes
Probabilistic sensitivity analysis (PSA)	Yes	Not applicable	Not applicable	Not applicable
Examples	• Efficacy • Treatment costs	• Transmission dynamic vs. discrete event simulations • Discount rate	• Model of an immune status (SIS vs. SIR) • Replacement	• Vaccination coverage • Risk group

Table 1 Types of uncertainty analyses [15, 20, 24, 37, 63, 65]

1.3 Health economic evaluations

This section focuses on aspects that require special approaches to preventive vaccinations. This section focuses on aspects that have to be handled particularly in HE for vaccinations. General aspects that are not explicitly or only briefly addressed are explained in more detail in the methods papers already mentioned [5, 6, 11]. This, however, does not constitute an endorsement of the approaches described in those papers.

1.3.1 Data basis

When selecting data that serve as the basis for EMs and HEs, careful attention must be given to quality. Only high quality data should be considered. Relevant guidelines must be followed especially when using secondary data [66]; relevant requirements should also be considered in expert consultations, see IQWiG, chapter 4.1.7 [6].

1.3.2 Clinical health care pathways

A clinical pathway explains treatment procedures in the respective indication in a chronological sequence and structures them according to sectors in the health care system. The clinical pathways and their associated costs should be illustrated according to the selection of comparators that are analysed within a model, see IQWiG, chapter 4.1.5 [6].

1.3.3 Perspectives

The societal perspective should be used in the base case, whereas the SHI perspective should be utilized in uncertainty analyses [9, 13, 14, 21, 28].

1.3.4 Costs

The literature addresses the question in depth of what costs should be considered in health economic analyses [5, 6, 13, 21, 67]. Depending on the perspective considered (see section 1.3.3),

various cost categories and their reimbursability should be taken into account (table 2). Direct costs are the resource consumption, assessed monetarily, of the indication of interest. They are subdivided into direct medical costs (e.g. costs of hospitalization or vaccination) and direct non-medical costs (e.g. transport costs to a hospital). *Direct costs*, such as copayments and surcharges to be paid by the insured individual and which are not reimbursed by SHI, are taken into account in the societal perspective. *Indirect costs* describe the loss of production due to sick leave and should be taken into account in the societal perspective regardless of the endpoint selected on the (health) effects side. When calculating the costs for sick leave, the friction cost approach should preferably be applied [68, 69]. Transfer payments are monetary payments, e.g. by the SHI to insured persons due to an illness. This includes sick pay, which should be taken into account in the SHI perspective.

Cost category Perspective	Direct medical costs	Direct non-medical costs	Indirect costs	Transfer payments
Society	Yes	Yes	Yes	No
SHI	Yes[4]	Yes[3]	No	Yes[5]

Table 2 Perspectives and relevant cost categories [6]

For illnesses that can be prevented by vaccination and that affect mostly children, benefits paid to their parental caregivers for missing work (sick pay due to illness of a child SHI perspective [transfer payment]) and indirect costs (societal perspective) should be taken into account (cf. tables 2 and 3).

[4] Direct costs, such as copayments and surcharges to be paid by the person insured and which are not reimbursed by SHI, are taken into account only in the societal perspective.
[5] Show separately from the other costs

Costs for sick leave (Societal perspective)	$₱ = \frac{\Lambda}{(employees \times 365)} \times AU$
Costs for sick pay (Transfer payment, SHI perspective)	$₮ = \frac{\Lambda}{(employees \times 365)} \times K \times k$
Costs for sick pay due to illness of a child (transfer payment, SHI perspective)	$₮_K = \frac{\Lambda}{(employees \times 365)} \times K_K \times k$
₱ =	Costs for sick leave per disease case
Λ =	Total compensation of employees per year in Germany [70]
AU =	Duration of sick leave ➔ 1 ≤ AU ≤ ł
ł =	Maximum duration of continued pay from employer, see EntgFZG, section 3, paragraph 1; the friction period (i.e. average vacancy time) is used for deaths [71]
₮ =	Costs for sick pay per disease case
K=	Duration of SHI sick benefits received in days ➔ BG ≤ K ≤ KG
BG =	Beginning of SHI sick benefits received
KG =	Maximum duration of sick pay, see SGB V, section 48, paragraph 1
k =	Adjustment coefficient for amount of sick pay, see SGB V, section 47, paragraph 1
$₮_K$ =	Costs for sick pay per disease case of a child
K_K =	Duration of illness of the child (age < 12 years) in days ➔ $1 \leq K_K \leq KG_K$
KG_K =	Maximum duration of SHI sick benefits received due to illness of a child, see SGB V, section 45, paragraph 2

Table 3 Calculating costs for sick leave and costs for sick pay

These costs should be calculated for the percentage of the working population that pays social insurance, or parental caregivers. However, in uncertainty analyses, the indirect costs can be calculated for all persons who are ill and/or parental caregivers, regardless of employment status, in order to consider also costs for sick leave of work not subject to social insurance payments, e.g. housekeeping.

If costs for a wide-reaching vaccination campaign occur, they can be included in sensitivity analyses in the relevant perspective as long as such 'sales'' costs are not already included in the price of the vaccine.

1.3.5 Health-related quality of life and quality-adjusted life years as a utility measure

Data on quality of life (LQ), measured in quality-adjusted life years (QALYs) are the basis for cost-utility analyses, and are used frequently in Europe [8, 14, 21, 72]. Whenever possible, valid data from Germany should be used; otherwise the reasons for using data from other countries and how potential adjustments were made should be presented. Uncertainty analyses of vaccine preventable diseases that mostly affect children should also include the LQ (measured in QALYs) of caregivers if adequate input data are available. If additional LQ data on increased feeling of security after vaccination (utility in anticipation) and/or LQ data on fear of adverse events after vaccination (fear of adverse events) are available, these effects should also be considered in uncertainty analyses.

1.3.6 Discounting

In health economics, the level and type of discounting is the subject of many analyses [8, 9, 13, 24, 25, 28, 40, 64, 73-83]. The most frequently applied approach is a uniform discounting that is constant over time. Hence, costs and benefits/utility[6] are given equal discount rates that are kept constant for the period covered by the model, see also IQWiG [6]. The (type of) discounting can have an enormous impact on the results of preventive measures, in particular on ICERs, as costs and health effects occur at different time points in a model. Therefore, the impact of the (type of) discounting on the results should be presented.

In base case analyses, the IQWiG approach (3% each for costs and benefit/utility, constant across time) should be used in order to treat curative and preventive interventions equally with regard to the discount rate in Germany [6]. In uncertainty analyses, besides the uniform and constant discount rates of 0% and 5% recommended by the IQWiG, additional analyses should consider: In models with a time horizon of >20 years a constant differential approach selected from the beginning (i.e. costs 3% and benefit/utility 1%), and a uniform approach that switches discounting rate from 3% to 1% after 20 years of the model time horizon for both costs and benefit/utility [84].

2 Methods of taking health economic evaluations into account in the decision-making processes of STIKO

2.1 Introduction

EMs and HEs are necessary in order to estimate future epidemiological and economic effects of a vaccination against infectious diseases at population level. It is the only way to identify the most effective and efficient vaccination strategy and to inform decision makers on the expected benefits of a vaccination to the population.

The focus of IQWiG's HEs[7] is not to develop a health care strategy regarding new pharmaceuticals, but rather to calculate a reimbursement price for a new pharmaceutical drug [85]. Beyond these differing aims, various circumstances lead the STIKO not to draw on the efficiency frontier approach used by the IQWiG in interpreting findings from HEs [6]. In 2010, these different circumstances were presented in a report commissioned by the Federal Ministry of Health (BMG) (p. 256 [7]):

(i) The efficiency frontier analysis is primarily a tool for price negotiations, but this is not the focus of the STIKO.

[6] This methods paper postulates the discounting of utilities regardless of how the corresponding data on quality of life were gathered.

[7] According to SGB V, section 139a, paragraph 3, number 2, the IQWiG can be commissioned to conduct cost-benefit assessments of pharmaceuticals in the context of services provided by statutory health insurance, also with respect to SGB V, section 35b. Furthermore, a cost-benefit assessment in accordance with SGB V, section 139b, paragraph 2 can be commissioned directly by the Federal Ministry of Health.

(ii) At least two products are necessary on the market for an efficiency frontier analysis[8]. That is very rarely, if ever, the case for vaccines because there are often only one or two suppliers of a certain vaccine.
(iii) Vaccinations are usually compared to the alternative of no-vaccination.

This section describes how findings from mathematical models to estimate the epidemiological effect and HEs should be processed and presented, and how STIKO can take findings from these analyses into account in its decision making process related to the development of vaccination recommendations.

2.2 Purpose of considering EMs and HEs in the STIKO decision making process

As explained in section 2.1, the aim of taking EMs and HEs into account is to enable STIKO to develop vaccination strategies that are effective (e.g. technical efficiency – which target groups should be vaccinated) and efficient (e.g. allocative efficiency – the most cost-effective results) [17, 76, 86-107]. EMs and HEs provide five benefits to achieve this aim:

(i) Modelling of future effects
(ii) Identification of critical input factors
(iii) Identification of the most efficient vaccination strategy
(iv) Budget impact analyses
(v) Decisions based on cost-effectiveness ratios using a willingness-to-pay threshold

Most European countries routinely take health economic evaluations into account when developing vaccination recommendations [4, 107, 108]. However, an official willingness-to-pay threshold (cf. benefit v) is explicitly used in only four countries (Ireland, UK, Poland, and Slovakia) [4, 109, 110]. As corresponding institutions in most other European countries, STIKO concentrates on benefits i, ii, and iii.

2.3 Presentation and documentation of findings from HE

The importance of uncertainty analyses has already been emphasized in section 1.2.12. For STIKO it is essential that uncertainty analyses are conducted, documented, and presented for all input factors and model structures. In addition, addressing potential uncertainties in terms of implementing or defining a vaccination strategy is relevant for the STIKO. These include, if relevant, uncertainty analyses in particular of:

- Vaccinating a specific age group and/or a comparison of various age groups
- Vaccinating the entire population or only risk groups
- Vaccination course (number of vaccine doses and vaccination intervals)
- Existence and extent of herd protection

[8] If the endpoint of an HE is 'cost per case prevented", for example, no efficiency frontier can be shown as long as vaccination is compared to non-vaccination.

- Consideration of booster and/or catch-up vaccinations
- Implementation strategy (e.g. first vaccinating risk groups and then the entire population)
- Level of vaccination coverage assumed or achieved

The presentation of findings from base case and uncertainty analyses should cover at least the following aspects:

- Discounted and undiscounted result figures
- Absolute figures and ICERs for all relevant endpoints
- ICERs of different points in time of the model in addition to ICERs for the entire model lifecycle
- Results from all relevant perspectives
- Cost-effectiveness acceptability curves[9]
- Best and worst case scenarios
- A report of the validation and calibration process
- Explanation of the quality of evidence of individual input data
- Discussion of the variation of results observed in uncertainty analyses

Transparency is imperative, and must be ensured in the software program code and in reporting.

2.4 Informal assessment

There is no willingness-to-pay threshold for ICERs in Germany (see section 2.2). Thus, an assessment of the results on such a threshold does not apply.

Results from EMs, HEs, in combination with other aspects that influence the STIKO decision making are taken into account in an 'informal assessment' [114]. If STIKO is in favour of a vaccination *after* a medical-epidemiological risk-benefit assessment (which may consider results from the EM), the most efficient vaccination strategy will be identified based on the results from the HE, and its feasibility and practicability will be analysed. ICERs provide information on the most efficient vaccination strategy. However, STIKO decisions give priority to first step, which includes key factor such as the number needed to vaccinate, the total number of health outcomes that can be prevented, or adverse effects of the vaccination.

[9] The x axis shows various ICER values; the y axis represents the probability of results from PSA that are below the corresponding ICER vaules (x axis) [111-113].

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Contribution

This methods paper is the result of a research project conducted at the RKI. The project heads were Dr. rer. medic. Dipl.-Volksw. Bernhard Ultsch and PD Dr. med. Ole Wichmann. The project leads were supported by a team of external advisers. The team of advisers consisted of Oliver Damm, MPH (Bielefeld University), PD Dr. med. Matthias Perleth, MPH (the Federal Joint Committee, staff office), and Prof. Dr. rer. pol. Jürgen Wasem (University of Duisburg-Essen). The findings of this project were presented and discussed regularly in the STIKO workgroup 'Methods'. Preliminary versions of this methods paper were reviewed by the STIKO workgroup. Further information on the project can be found at www.rki.de/steering.

Acknowledgements

We would like to thank the project advisers for their valuable contributions, the Federal Ministry of Health for financing this project, and the RKI, in particular staff of the immunization unit. Special thanks go to the experts who participated in the international workshop and the national symposium.

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