Standards on how to parameterise models via published literature

Input of the LBI-HTA for IFEDH work package 4.2

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Projektteam

Management: Dr. rer. soc. oec. Ingrid Zechmeister-Koss, MA

Content: Dr. rer. soc. oec. Ingrid Zechmeister-Koss, MA

Addtional contribution

External review: DI Patrick Einzinger

Internal review: P.D. Dr. phil. Claudia Wild

Correspondence: Ingrid. Zechmeister, ingrid.zechmeister-koss@htalbg.ac.at

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Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Wien
http://hta.lbg.ac.at/

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Decision-analytic models within HTA on the one hand require qualitative (structural) knowledge on the disease under consideration (e.g. spread of a disease and its influencing factors, which type of costs are incurred by the disease and where). On the other hand modellers need quantitative data to define the model parameters.

decision analytic models require qualitative and quantitative information

Examples for the latter are data on the prevalence of a disease in a defined population at the starting point of the model, infection rates in cases of infectious diseases or costs for treatment. The more precise these data are the more precise model results will be obtained, because uncertainty is minimised.

e.g. prevalence data

The aim of work package 4.2. is to define recommendations on how to parameterise models on the basis of secondary data including challenges and possible solutions.

how to obtain quantitative information from secondary data?

2 Research question

The project group defined the following research questions:

research questions

- What type of data are published in clinical studies on the diseases to be modelled in IFEDH (especially on infectious diseases) and on drugs/vaccination?
- For which types of model parameters is it appropriate to do a (systematic) literature search?
- What is the recommended strategy to search for literature on model parameterisation? Is the identification of literature different from standard search procedures for effectiveness of an intervention within an HTA?
- Is it possible to obtain data from a clinical study in a less aggregated way as they are presented in publications (e.g. total number of patients with improved health status after drug treatment in contrast to presentation of this group disaggregated according to age or smoking status)?
- What are the required characteristics for data obtained from published literature? For example, should data be presented with their confidence intervals in contrast to point estimates only?
- To what extent can a literature search be helpful to gain qualitative knowledge (for issues defined in work package 4.1)? What type of literature is useful (text books, literature on basic research etc.)?

3 Aim

The aim of this report is,

aims:

- to provide an overview on methodological standards concerning the utilisation of different data sources for defining model parameters. The focus will be on data sources from secondary literature (published clinical studies or meta-analyses). Other types of secondary data (e.g. routine data) will only be described briefly for reasons of completeness because they are addressed in another work package (WP 5).

identifying standards on utilising data sources for model parameters

- to translate the generic standards concerning relevant data sources from manuals into the case study 'Human papilloma virus vaccination modelling' (HPV-vaccination modelling) including data on screening, vaccination, history of disease etc. This is to provide information for work package 8 (proof of concept).

application in case study

4 Method

- HTA-manuals, country-specific guidelines on economic evaluation and published methodological standards on modelling are analysed. Recommendations on possible data sources, on the identification of data and on issues related to the correct handling of the data are extracted and summarised.

HTA-manuals and guidelines are analysed

- The information sources used for this part of the report is all the literature from work package 1.2 (where HTA-manuals have been identified by electronic and by hand search) as well as the overview on country-specific health economic evaluation guidelines on the ISPOR-webpage (www.ispor.org).

information sources: earlier work and ISPOR webpage

- We include documents in English or German language that are related to ‚western' industrialised countries and that contain information on data sources for modelling that goes beyond a mere listing of data sources.

language: German and English

- The recommendations are contrasted with the data identified in the ‚HPV-vaccination literature'. This will be alongside the parameters that are required for modelling HPV-vaccination. Only parameters that are defined out of data in published literature are described. Parameters that are primarily based on further secondary data (routine data, official national statistics) are not included in the detailed description.

contrasting standards with case study 'HPV modelling literature'

Data that are found in the literature may not be in the format required for the model and may need to be adjusted. Several methods exist on how to adjust data by modelling. Information on these methods (e.g., methods for incorporating estimates of treatment effectiveness from clinical trials into a model) are addressed in a separate IFEDH report.

standards on further data management are addressed in separate document

5 Potential data sources

5.1 Identified literature

13 documents selected

Overall 43 references were available (figure 5.2-1). 13 documents were selected for our purpose. One source out of these 13 documents [1] has been identified in the references of the primary documents and has been included because it specifically addresses the issue of data sources selection for modelling, although it is not a manual or guideline in its strict sense.

rest excluded

The remaining 30 documents were excluded because they did not contain enough information for answering our research questions (n=18), they came from 'non-western' countries (n=10) or they were written in a language other than German or English (n=2).

5.2 Potential data sources for models

data sources will be described in following chapters

In the documents a variety of data sources are mentioned that may be relevant for defining model parameters. These will be classified and described in more detail in the following chapters including information on their potentials and limitations. Table 5.2-1 summarises the information.

overall limited information available

Overall, neither document provides extensive information on the issue in question. Mostly, information is restricted to listing the different data sources including a brief description on their advantages and disadvantages.

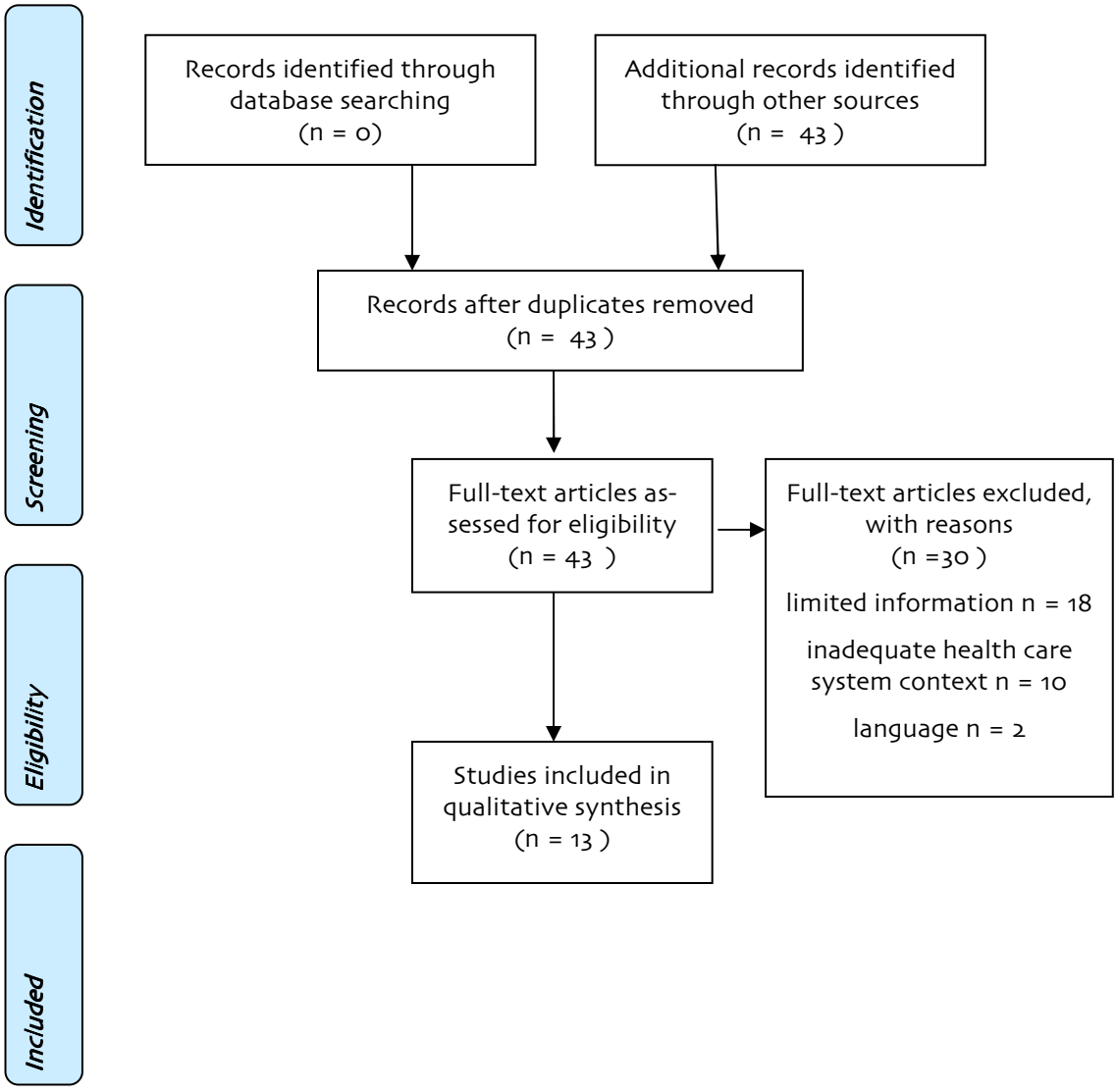


Figure 5.2-1: PRISMA Flow Diagram for the selection of literature

5.2.1 Clinical studies and meta-analyses

Randomised controlled trials (RCTs) and meta-analyses

for efficacy/effectiveness: RCTs and meta-analysis, yet low external valdity

Experimental clinical studies (RCTs) and their meta-analyses are regarded as first choice data source for defining parameters related to the efficacy and effectiveness of a technology. However, their main limitation, which is the limited external validity and the restricted generalisability of results to the real world setting, is also recognised. Yet, in the absence of large scale 'real world RCTs' [2], classical RCTs are still the preferred source for effectiveness data compared to other data sources.

RCTs also for limited cost information

In addition to efficacy/effectiveness information, RCTs may also be used to obtain information on costs, however two frequent problems in using clinical studies for costing information are mentioned: Firstly, they may not cover all relevant cost-categories and secondly, the studies may not have been powered to detect cost differences [3]. Furthermore, in one manual it is pointed out that the simple currency conversion of values found in the literature is not accepted [4] which addresses the limitation of transferring international cost data to one's own jurisdiction.

control groups of RCTs for baseline probabilities

Another guideline mentions that the control group of an experimental study may be used to obtain baseline probabilities on the natural history of disease [5].

meta-analysis if more than one study available, yet bias possible

While meta-analyses are explicitly and repeatedly mentioned as important data source for efficacy/effectiveness issues in those cases, where more than one study is available, the danger of using low quality meta-analyses (e.g. those that include studies selectively or those that include heterogeneous studies) is also pointed out [1, 6].

In one reference, meta-analyses are presented as source for calculating transitional probabilities and as source for obtaining information on treatment failure [1]. However, the authors do not explain the method to be applied in detail.

Further clinical studies

further clinical studies especially for 'real world' safety data…

Apart from RCTs and their potential to define the efficacy of an intervention, a number of further clinical studies are mentioned in the documents as a valid source for defining model parameters: data for parameters on test accuracy of a diagnostic test may be obtained from test accuracy studies, data for defining prognostic parameters on morbidity or mortality may be obtained from prognostic studies, data on incidences of future events can be found in risk-factor studies. Observational (clinical) studies may be a valid source for safety data, they provide 'real-world' data (for effectiveness) and data on compliance. The disadvantage that has been stated for the latter is that there is little control over confounding and certain types of bias. Furthermore, observational studies may be of limited use if they lack a control group [6].

…and possibly health state values

Finally, one manual mentions that data on 'health state values' (values for different health states in the model from 0 to 1 for the calculation of QALYs) may be derived from different clinical studies, however these should be treated with utmost caution and only be used if measured with the same instrument and in a similar patient population [4].

5.2.2 Epidemiological studies

epidemiological studies for extrapolation, current practice and info on natural history of diseases

The terms 'clinical studies' and 'epidemiological studies' have not been explicitly defined in the manuals. Hence, it is unclear what the term 'epidemiological studies' exactly refers to and if/how it is to be distinguished from clinical epidemiological studies. Nevertheless, the term 'epidemiological studies' has been mentioned in 3 manuals where they are regarded as a useful source to extrapolate data from clinical trials and for identifying valid surrogate endpoints for patient relevant endpoints. Additionally, they may yield information on the current medical practice and they can be used for natural history data from which baseline probabilities can be obtained [5].

limitation: confounding

However, they are limited by confounding and certain types of bias which is why they are not recommended for defining parameters on efficacy or effectiveness. When epidemiological studies are used to define predictive functions, the interpretation of these functions and the validity of transferring fixed risk functions onto the modelled study population need to be explained and justified.

5.2.3 Routine data

many manuals mention routine data

Eight out of the 13 selected documents explicitly mention several types of routine data. The terms that are used are 'claims data', 'retrospective data sets', 'databases', 'Abrechnungsdaten', ' Prozessdatenbanken', 'national data on healthcare resource groups (HRGs)', ‚Routinedaten', 'validated databases' or 'administrative and accounting databases'. It is recommended that those data are assessed for relevance and completeness before they are used for modelling purposes.

advantage: large number of patients, data for resource use/costs

disadvantage: model population may not be depicted in data

Authors mention as advantage that these sources contain data on large number of patients and may be appropriate if the relevant target population in the model is sufficiently depicted in the data (via diagnostic codes). They are also regarded as helpful for defining treatment paths or obtain information on the behaviour of patients. Hence, they are a valuable source to obtain data on resource use or costs. However, they may as well be problematic in use if the definition of the model population includes parameters (e.g. clinical results, specific patient characteristics) that are not coded in the database.

5.2.4 Registries

registries represent real life situation: e.g. for predictive functions, probabilities

Registries are mentioned in three manuals only [3, 7, 8], although the term 'observational studies' that appears in other documents may also refer to registries. Authors point out that registries represent a real-life situation and may be helpful for defining predictive functions that describe the association between clinical event and resource use, quality of care, sick leave etc. Additionally, disease registries are mentioned in context with defining probabilities of events. Yet, before using registries for defining model parameters, it is pointed out that the access need to be verified and the relevance of the registry-data for the model parameters in question must be assessed.

5.2.5 Compiled statistics

compiled statistics relevant for demography, health behaviour, mortality

Four out of the 13 sources mention compiled statistics, such as data from the 'Central Statistical Office' [2], 'health care system data' [9] or national and regional health statistics [7] as a data source for modelling. These data may contain relevant information on demography, health behaviour or risk factors and they are the primary source to define all-cause mortality (from life-tables). Additionally, they may provide information for costs, such as data on median income to calculate productivity costs. Before the data from those sources are used they have to be assessed in terms of quality and relevance for the model and their origin must be transparently stated.

5.2.6 Expert opinions

expert opinion is legitimate source for qualitative information, not for defining efficacy

In the majority of the documents expert opinions are explicitly mentioned as a legitimised data source, especially in situations where data are missing, conflicting or insufficient. However, in a number of documents it is clearly stated that expert opinion is not accepted to define parameters related to efficacy or safety of a technology. One manual accepts expert opinion to define effectiveness on the basis of published data on efficacy, if no published data on effectiveness are available [10]. In the majority of the documents expert opinions are regarded as appropriate only for defining the model structure or to obtain qualitative information on the disease or the technology in question while such data is regarded as hardly appropriate for defining final input parameters. They may at most be a valid source for defining parameters that do not affect the results importantly [11].

should be derived via formal and transparent methods

In any case, there is consensus across all manuals that the use of expert opinions has to be justified and is only accepted as 'last resort' if no better data are available. Furthermore, all documents make clear that the use of expert opinions has to be described transparently (number of experts asked, selection process etc.) and opinions should ideally be derived via formal methods such as 'Delphi' or 'Nominal Group techniques'. If parameters are defined on the basis of expert opinions they must undergo sensitivity analyses to control for uncertainty. Not least, it has been stressed that the collection of expert opinions may be a time-consuming task if done correctly [1].

5.2.7 Further sources

further sources possible (textbooks, medical records etc.)

There are number of further data sources that are mentioned in the 13 reports. These, firstly, include textbooks that may yield information on the doses of drugs, drug prices and reimbursement percentages[1]. Another source that is mentioned in three documents [1, 4, 6] are medical records that have the advantage of depicting the 'real-life situation' (e.g. for resource use information), although using them may be time consuming because their information cannot be entered directly into statistical data processing.

Data from the consumer-price index and on purchasing power parities are mentioned as valuable source for inflating cost data and converting currencies. Furthermore, official tariffs lists and lists on standard costs are mentioned as data source for cost calculation without providing further details on their characteristics.

'Finally, the Canadian manual [8] mentions clinical practice guidelines as a source for obtaining resource use data.

Table 5.2-1: Overview of information on how to parameterise models in guidelines and manuals

	Weinstein et al. (2003) [11]	**Philips et al. (2004)[5]**	**Nuijten (1998) [1]**
Recommended Method for data identification	Systematic literature search;	Searching should be systematic and efficient (focus on those parameters that are expected to have the largest influence on the model results); method of data identification needs to be transparent;	Not stated
Potential data sources as stated in the documents	„all evidence may be legitimate" (incl. expert opinion);	Clinical studies, epidemiological/observational studies, retrospective datasets, expert opinions, health statistics (e.g. life tables), consumer price index, purchasing power parities;	Clinical studies, meta-analyses, databases[1], medical records, Delphi-methods, others (e.g. textbooks, official tariff lists);
Required data characteristics	Ranges (ie, upper and lower bounds) should accompany basecase estimates of all input parameters for which sensitivity analyses are performed. Data sources and results should not be rejected solely because they to not reach generally accepted probability thresholds defining 'statistical significance' (e. g., p > .05);	Best available data should be used for every parameter; clinical trial data should not always be regarded as the gold standard for modelling; data can be incorporated as point estimates or as a distribution (will be influenced by how analysts evaluate parameter uncertainty;	Not stated
Recommendations on the correct handling of the data	Expert opinion is a legitimate method for assessing parameters, provided either that these parameters are shown not to affect the results importantly or that a sensitivity analysis is reported on these parameters. Expert opinions need always be made transparent and should be derived from formal methods such as Delphi or Nominal Groups techniques;	Quality and relevance of all data must be assessed; using accepted quality check lists is recommended; When using retrospective data, completeness of the data set should be assured including an assessment of the population covered by the data in comparison to that in the model; retrospective data are a common source of resource utilisation estimates; if expert opinions are used, standards include documentation of the details of the inclusion criteria for experts, sample size, the types of questions asked, the method for data collection and number of iterations; Hierarchy of data should be secondary to the identification of a hierarchy of parameters in the model; The strengths and weaknesses of each data source should be described;	Not stated
Advantages of single data sources	Not stated	Epidemiological/observational studies or the control group of an experimental study may be used to derive baseline probabilities on the natural history of a disease; It is often appropriate to derive relative risks (or odds ratios) between treatment options in trials and to superimpose those onto baseline probabilities derived from other sources	Meta-analyses: may be used in the definition of transitional probabilities (based on efficacy measures for initial treatment) (e.g. when the comparator in a pharmacoeconomic analysis is not the same as the comparator in a clinical trial); may provide data on treatment failure;

[1] refers to „claims databases and clinical outcome databases"

		(which are usually population based);	Databases: may contain a lot of detailed information on both, clinical and economic outcomes for large number of patients; high external validity; Delphi Panel technique: appropriate in situations with missing, insufficient or conflicting data;
Disadvantages of single data sources	Not stated	Clinical studies: low external validity, limited duration of follow-up;	Clinical studies: low external validity, units of health care that are used and collected may not be complete; often not powered to detect cost differences between groups and short follow-up; Meta-analyses: as clinical studies + risk of publication bias and inclusion bias; databases: rarely sufficient to draw definite conclusions about relative effectiveness; format of information may not fit the structure of the model (e.g. coding of ICD-10 diagnoses driven by reimbursement issues); medical records: information cannot be entered directly into statistical data processing (time consuming); Delphi Panel technique: time-consuming; compromise between scientific rigour and need for structural information;

	Austrian HTA manual (2011) [7]	IQWIG modelling manual (Germany) (2009) [3]	NICE (England/Wales) (2008) [12]	KCE (Belgium) (2008) [4]
Recommended method for data identification	Not stated	Systematic search	For all parameters a systematic consideration of possible sources is required, and the selection of sources to justify a particular outcome must be avoided;	Systematic literature search for identifying clinical studies;
Potential data sources as stated in the documents	Clinical studies, prognostic studies, risk factor studies, epidemiological observational studies, disease registries, studies on compliance/coherence, claims data, national and regional health statistics, expert opinions;	Clinical studies, epidemiological studies, process databases (Prozessdatenbanken)[2], registries[3],, compiled statistics[4], expert opinions;	Sources might include cohort-studies, randomised trials (head-to-head trials in particular), meta-analyses, non-randomised trials, cross-sectional surveys, national data based on healthcare resource groups (HRG), public price list;	Clinical studies, validated databases, literature (peer-reviewed, no slides from presentations or abstracts), prospective observational studies, databases, patient charts, reimbursement scheme, 'FOD Volksgezondheit/SPF Santé Public', expert opinions (not accepted for defining probabilities or outcomes, if this information is available from published literature);
Required data characteristics	Not stated	Depends on model parameter;	For continuous variables mean values should be presented; for all variables measures of precision should be detailed;	Data should be presented with their 95% confidence or credibility interval;
Recommendations on the correct handling of the data	Selection of data needs to be justified; data on efficacy should be from clinical studies, on test accuracy of a diagnostic test from diagnostic studies, on prognostic parameters for morbidity and mortality from prognostic studies, on incidences of future events from risk factor studies, on the frequency of events from epidemiological studies or disease registries, on therapy adherence/coherence from studies on coherence/adherence, on resource utilisation from routine data/claims data, on demographic parameters from official health statistics; miss-	Required level of evidence depends on model parameter (e.g. data on efficacy require high level of evidence); Clinical studies: pooled data or meta-analyses may be used; Epidemiological studies: interpretation of predictive functions and validity of transferring fixed risk functions to the modelled population need to be explained and justified; Process databases: relevance of its data for modelling needs to be assessed; Registries: access must be guaranteed and relevance of registry-data for model must be assessed; Compiled statistics: sources need to be stated;	As much detail as possible on the data used in the analysis should be provided; Estimates of treatment effects should be based on the results of the systematic review; Individual patient data are preferred, if available, for the estimation of subgroup-specific parameters;	Models should be based on data from clinical studies comparing the study medication and the comparator, on data from validated databases and/or data from literature; use of health state values from different clinical studies should be treated with caution (only if measured with same instrument and in similar population); use of expert panels is subject to specific conditions; preferably only as complementary source (method described in detail in the manual's appendix); Manual refers to ISPOR model-

[2] Databases that are derived from routine processes (Abrechnungsdatenbanken)

[3] Observational studies that systematically collect (a limited number of) data from a large number of patients who have been treated under routine conditions

[4] Health statistics that have been compiled by governments from census or survey data

	ing data may be obtained from experts if controlled for uncertainty in sensitivity analyses;	quality and relevance needs to be assessed; Expert opinions: Justification for and description of method used to obtain expert opinions needs to be stated;		ling-guideline for further quality issues [11];
Advantages of single data sources	Not stated	Observational studies: appropriate for extrapolation of clinical study-data and for identification of valid surrogate endpoints for patient relevant endpoints; Process data bases: contain data on large number of patients; appropriate if relevant target population in model is sufficiently depicted in the data (via diagnostic codes); helpful for defining treatment paths, behaviour of patients (for cost calculation); Registries: represent real-life situation; may be helpful for defining predictive functions that describe the association between clinical event and resource use, quality of care, sick leave etc.; Compiled statistics: may contain information on demography, health behaviour and risk factors; useful to define all-cause mortality; Expert opinions: restricted use for defining the model structure and assumptions;	Not stated	Meta-analyses of clinical trials may increase the reliability of the clinical evidence and thereby validity of the model;
Disadvantages of single data sources	Not stated	Clinical studies: for cost estimates only of restricted value (e.g. incomplete information on issues of care that may be relevant for total costs, not enough power to detect cost differences); Process databases: problematic if the definition of the model population includes parameter (e.g. clinical results, specific patient characteristics) that are not coded in the database; Expert opinion: for defining final input parameters hardly ever appropriate;	Trial data may not be sufficient to quantify baseline risk;	

	Poland Agency for HTA (2009) [13]	CADTH (Canada)(2006) [8]
Recommended method for data identification	Systematic search for key parameters;	For key parameters: systematic search; non-systematic search needs to be justified;
Potential data sources as stated in the documents	Clinical studies, observational studies, routine databases, list of standard costs, published literature;	RCTs, observational studies, administrative databases, disease registries, expert opinions, standard cost lists, clinical practice guidelines, systematic reviews and/or meta-analyses, administrative and accounting data;
Required data characteristics	Not stated	Data can be incorporated as point estimates or as distribution (in case of probabilistic sensitivity analysis);
Recommendations on the correct handling of the data	If experts' opinions are the source of input data, the methods of obtaining the data should be described;	All data should be reported and their sources identified; details of the data should be described (e.g. from which data were derived and to which the results apply); data limitations should be made transparent and the methods for handling them described; Manual refers to Philips et al. [5] and Weinstein et al (ISPOR document) [11] for further quality issues;
Advantages of single data sources	Results of effectiveness obtained from observational studies are better than experimental results assessed in a systematic review, which should be treated with utmost care;	Systematic reviews and meta-analyses can produce high quality data for model parameters, and add to the credibility of economic evaluations; they also provide useful information for analysing uncertainty surrounding the relevant estimates;
Disadvantages of single data sources	Not stated	Not stated

	Alves de Silva et al. (Portugal) (1998) [10]	Szende et al. (Hungary) (2002) [2]	AMCP (USA) (2009) [14]	PHARMAC (New Zealand) (2007)
Recommended Method for data identification	Not stated	Systematic search for effectiveness	systematic search for key model parameters	"All evidence should be obtained systematically"
Potential data sources as stated in the documents	Clinical studies and meta-analyses, population-based epidemiological studies, hospital-based epidemiological studies, expert panels;	Large scale real-life RCTs or systematic reviews, clinical studies, non-experimental studies, expert opinions, data from the Information Centre for Healthcare, data from Central Statistical Office;	RCTs, observational studies, health care system data, expert opinions;	Effectiveness: published RCTs, meta-analyses and observational studies; unpublished data from clinical studies; expert opinions; data from medical records and case reports; All-cause mortality: life tables; Long-term outcomes: observational studies or other clinical studies; Costs: Pharmaceutical Schedules, clinical studies (for doses), Health Information Service; Utility values: several databases on health-related quality of life data;
Required data characteristics	Not stated	Not stated		Not stated
Recommendations on the correct handling of the data	For the epidemiology of a disease: population-based epidemiological studies should be used; if such data are unavailable, hospital-based or regional epidemiological studies may be used; For effectiveness: RCTs or meta-analyses on efficacy are to be preferred (adapted with data on effectiveness – e.g. from observational studies); Prospective data are to be preferred in contrast to retrospective data; Expert panels should be considered as last resort and cannot be used to estimate efficacy (only effectiveness on the basis of real efficacy data or for diseases, syndromes or conditions with a low prevalence or incidence); Data on the current medical practice can be derived from epidemiological studies or cross-sectional studies;	Ideally, effectiveness data should be derived from large, randomised, real-life, cost-effectiveness studies and their systematic reviews; in practice, these rarely exist ->alternative sources are required; Expert opinion is not substitute for sound evidence but may help to interpret the outcomes of the studies, to frame the context and to predict resource utilisation patterns; Cost data should be derived from the ‚Information Centre for health care', average salary values should be taken from 'Central Statistical Office';	For efficacy and effectiveness: RCTs, for safety: RCTs and observational studies; economic and demographic parameters: health care system data; expert opinions are not generally acceptable, esp. For key effectiveness or safety variables;	Not stated

Advantages of single data sources	Not stated	Not stated	Not stated	RCTs: external influence minimised -> effect is attributable to intervention alone; Meta-analysis: useful when results conflict between trials, when inappropriate comparators are used or when a trial consists of only one treatment arm; single trial may be insufficiently powered; Observational studies: high real world relevance; allow observation of treatment on compliance and treatment switching patterns; Expert opinion: clarification of unreliable, conflicting or insufficient clinical information in the literature; Case reports and medical records: high real world relevance;
Disadvantages of single data sources	Not stated	Not stated	Not stated	RCTs: poor external validity; often short time spans; may be subject to publication bias; Meta-analysis: publication and inclusion bias; may be difficult to assess validity; incompatible trials may be included; Observational studies: lack of control over confounding factors; underlying biases; lack of control group; Expert opinion: subject to selection bias; Case reports and „medical record": high risk of bias; small patient numbers;

6 Standards for data identification

systematic literature search is standard for data identification

As outlined in table 5.2-1 the standard method for identifying data in published literature is the systematic (in contrast to selective) literature search which is mentioned in every manual that describes how to obtain data. The reason behind the systematic search is to minimise (selection) bias as much as possible.

resource constraints may limit systematic search to key parameters

However, the documents vary in the extent to which various model parameters need to be based on systematic literature search. By referring to resource constraints, several manuals limit the requirement for a systematic search to 'key model parameters'. While it has usually not been defined which parameters are to be seen as 'key parameters', parameters on efficacy or effectiveness are mentioned in most of the documents as those for which data must be obtained via systematic search. Philips et al. [5] define the 'key parameters' as those that are expected to have the largest influence on the model results.

good guidance in Philips document

Furthermore, Philips et al. [5] offer a comprehensive overview on valid data sources for a variety of parameters (baseline event rates, health-related quality of life and its valuation, resource use and unit costs, relative treatment effects, other parameters). Moreover, they provide guidance to define 'searchable questions' and (in the appendix of their document) they present search strategies for various parameters from a case-study. The approach is not different from systematic search techniques known from HTA-manuals.

search for any data needs to be transparent

Generally, all documents agree on the standard to present the search for any model data transparently and to state the sources used. The exclusion of (appropriate) available and known data sources needs to be explicitly justified.

no guarantee for avoiding any bias

Some manuals point out that a systematic search does not guarantee to avoid all sorts of bias. The main problem arises if studies have been published selectively in the first place (publication bias).

7 Recommendations on the correct handling of data

hierarchy of data should be secondary to hierarchy of model parameters

While the documents agree on the requirement to use the best available data for every parameter, some also make clear that not every parameter requires data from highest level in the evidence hierarchy (RCTs or meta-analyses). As Philips et al. [5] point out, the hierarchy of data should be secondary to the identification of a hierarchy of parameters in the model. In other words, clinical trial data should not be regarded as the gold standard for every single model parameter.

recommendations:

Concerning potential data sources for key model parameters, the following recommendations can be summarised from the documents (see also table 5.2-1):

high level of evidence for efficacy, effectiveness and safety: RCT, meta-analysis

- Firstly, parameters that deal with the efficacy, effectiveness or safety of a treatment/preventive measure need to be based on data that are at the highest level of the evidence hierarchy (RCTs or meta-analyses). However, both safety and effectiveness data may also be obtained from observational studies/disease registries as they represent the real-life situation better than clinical trials.

Baseline probabilites/data on natural history from observational studies/registries

- Secondly, parameters that are related to baseline probabilities and to the natural history of a disease may be derived from observational studies/disease registries or from the control group in clinical studies.
- Observational studies are also a potential source to parameterise long-term effects (for extrapolating data from clinical trials).

quality of life data from primary research or (with limitations) from published clinical studies

- Data on health related quality of life and their valuation are primarily to be obtained by primary data collection or from existing national data (e.g. on health state valuation). Two documents provide secondary data sources for those data, however limitations in terms of transferability have been stressed and caution has been pointed out when combining health related quality of life data and/or their valuation from various sources.

demographic data from national statistics

- Parameters on demographic characteristics (including all-cause mortality) can be derived from national health statistics. For defining all-cause mortality, life-tables are recommended in various manuals.

resource use and cost data from routine data, practice guidelines and expert opinions

- Data on resource use as well as on unit costs need to be context-specific and will therefore hardly be found in published literature. Appropriate data sources for the former will rather be routine data, clinical practice guidelines and expert opinions. Published clinical studies may in some cases be a potential source of information for resource use patterns, although severe limitations in terms of transferability from one jurisdiction to another or from the study-context to the real-life context need to be taken into account.
- Where data sources on unit costs have been described in the documents, they are also rather country-specific such as standard price lists or national data on health care resource groups.

data should be presented with upper and lower bounds

Three documents [5, 11, 12] present details on required data characteristics. For example Weinstein et al. [11] points out that ranges (ie, upper and lower bounds) should accompany basecase estimates of all input parameters for which sensitivity analyses are performed. Similarly, the NICE guideline [12]

states that for continuous variables mean values should be presented and that for all variables measures of precision should be detailed. Finally, data sources and results should not be rejected solely because they to not reach generally accepted probability thresholds defining 'statistical significance' (e. g., $p > .05$).

quality assessment via checklists required before using data for models

Overall, the methodological guidelines stress that data have to be assessed in terms of relevance and quality before they are used for defining model parameters. For quality assessment specific quality checklists that exist for various types of data (e.g. data from clinical trials, data from cohort studies) are recommended. In any case, data limitations and how these were dealt with (e.g. by applying different types of sensitivity analyses) need to be described transparently.

8 Conclusion of literature search

three subjects addressed: data sources, data identification, data processing

Concerning parameterising decision analytic models, three different subjects have been addressed in the previous chapters: Firstly, generally available potential data sources to define model parameters have been identified. Secondly, standards on how to identify or search for those data have been summarised and thirdly, recommendations on the correct handling of such data have been presented.

quality of model depends on correct identification and handling of data

Data identification and choosing appropriate data considerably contribute to the overall quality of parameters used in a model. In other words, adhering to standards in choosing appropriate data sources and in the further processing of data will greatly improve the quality of model parameters and, hence, the quality of the model per se.

terminology of data sources in manuals not always clear

Generally, it needs to be noted that the terminology used for the different types of data lacks consistency and due to the absence of clear definitions of the terms used it has not always been clear what type of data the authors are exactly referring to. For example clinical studies and observational studies are mentioned as two different data sources [7]. However, observational studies may also be defined as a subtype of clinical studies. It has become clear that in many cases authors use the term 'clinical studies' when they mean randomised controlled clinical trials (that is experimental clinical studies).

The research questions from chapter 2 can be answered in the following way:

core secondary data sources: published RCTs and meta-analysis, further clinical studies

The primary data sources for model parameters in the literature are RCTs and meta-analyses for efficacy, effectiveness and safety issues. Various types of (clinical) epidemiological studies are appropriate for effectiveness and safety issues, for data on the natural history of disease, for long-term effects and for epidemiological data (e.g. mortality rates, life-expectancy).

further secondary data sources and expert opinions also relevant

Additionally, a number of further sources of secondary data have been mentioned, being routine data and national statistics. Finally, expert opinions have been addressed throughout all manuals, however, with pointing out their limitations.

data from literature should be based on systematic literature search

Secondary data from published literature that are used for parameterising models, should as much as possible be based on systematic literature searches. Yet, the limitations in resources have been acknowledged and suggestions have been made to restrict the systematic search to efficacy data and to those data that are used for model parameters that are likely to have the largest influence on the result. The technique of the literature search does not differ from standards in literature search in HTA general.

method like in HTA

using primary data from published clinical studies not addressed but possible

The manuals do not address the issue of using primary data from published clinical studies, however, there are examples elsewhere, where such data have been used and pooled for further research purposes such as the 'Cholesterol Treatment Trialists Collaboration' [15].

limited information on specific data characteristics

With respect to required data characteristics, the manuals provide very limited information. Yet, it has been mentioned in several documents that ranges are required for those data that are later on used for sensitivity analyses in the model.

Dealing with qualitative information from published literature not addressed

The manuals do not address the issue of using published literature for qualitative information on the model. Qualitative information has, however been mentioned in context with expert opinions where qualitative rather than quantitative information may be obtained.

open questions will be dealt in part two of report

Questions no. 1 and 4 (type of data that are available from clinical studies; can data from clinical studies be obtained in a less aggregated way as presented in the publication) will be addressed in the following chapters.

9 Applying the methodological standards to 'HPV-vaccination modelling'

several secondary data sources required for models

In the previous chapters it has been shown that a variety of data sources are needed to define model parameters appropriately. While many of those include secondary published literature, several further secondary data sources (such as routine data) have been mentioned in the manuals.

standards from manuals will be applied to HPV-vaccination case study

In the remainder of the report, the information from the previous sections on potential data sources will be applied to the case of 'HPV-vaccination modelling' for using it later on in work package 8.

required information categories will be described and data for those will be identified in the literature

The following sections will systematically describe the information categories that are relevant for the planned modelling exercise. In relation to appropriate data sources from chapter 5, potential data sources for the 'HVP-vaccination model' will be identified and data that are considered as relevant will be extracted. Data extraction will, however, be restricted to secondary published literature whereas data that from other secondary data sources will not be addressed. Readers are referred to work package 5 for further information on the latter. Finally, the relevance and limitations of the data identified will be discussed and the overall process and the experience gained will be contrasted with the methodological standards obtained from the manuals in the previous chapters.

further secondary data not addressed

literature from earlier projects will be used

Where appropriate, literature that has already been identified via literature search in a 2011 updated 'HPV-vaccination project' at the LBI-HTA (see http://hta.lbg.ac.at/de/projekt_detail.php?iMenuID=66&iProjectID=28) will be used as source for data. These sources include published studies until July 2011. Only in those cases where additional literature is required, there will be a separate literature search. For reasons of resource constraints, this will, however, not be a systematic search but it will rather be restricted to a basic search for most recently published studies, reviews or meta-analyses in PubMed. This is because the aim of this chapter is to provide examples for the type of data and their characteristics as they can be found in the literature rather than a full overview of published secondary data for every single model parameter. Furthermore, due to resource constraints the studies will not be assessed for quality.

data will not be assessed for quality

9.1 General overview on the HPV-modelling concept for work package 8

HPV-vaccination introduced in several countries

HPV-vaccination has been introduced in numerous countries with the aim to prevent HPV-infection from two to four HPV-types and diseases that are related to persistent HPV infection.

in WP8: update of earlier HPV-vaccination model

The aim of the modelling exercise in work package 8 is to update the disease model on HPV-infection that has been used by the LBI-HTA in 2007 [16] with the latest epidemiological evidence, with evidence on the efficacy of the vaccination and on sexual behaviour. Furthermore, the model will be used to compare HPV-vaccination with additional screening alternatives and to predict additional health outcomes and costs.

alternatives compared in the model

The following alternatives will be analysed

- Screening only 'status quo'[5]
- Screening only 'status quo' + HPV-vaccination of 12-year old girls
- Screening only 'status quo' + HPV-vaccination according to Austrian vaccination recommendations[6]
- Screening only 'new'[7]
- Screening only ‚new' + HPV-vaccination of 12-year old girls
- Screening only ‚new' + HPV-vaccination according to Austrian vaccination recommendations

outcome parameters addressed

The following outcome parameters will be analysed

- clinical parameters
  - cervical carcinoma incidence
  - cervical carcinoma mortality
  - precancerous lesions (and the number of conisations that are linked with them)
  - life years gained
- economic parameters
  - incremental costs (direct costs only)
  - incremental cost-effectiveness ratios
  - budget impact

model is basis for further work on cancer prevention

The model should enable future work to develop an overall appropriate prevention strategy on cervical cancer in Austria considering different prevention alternatives.

Based on the previous work on HPV-vaccination modelling in Austria, a number of data categories and specific data requirements have been identified that will be described in the following sub-chapters.

9.2 Demographic data

demographic data need to be identified in national statistics

Demographic data are required for defining the size of the various age cohorts that are to be vaccinated and screened over the defined time horizon and for linking the dynamic of the Austrian population with the transmission

[5] Status quo is related to current practice in terms of screening interval, opportunistic screening and diagnostic procedures

[6] Vaccination of girls and boys at the age of 9 years, catch-up boys until 15 years and girls/women until 26 years

[7] Increased screening participation based on experience in countries with well-running organised screening; screening (80%); interval according to guidelines and experience in countries with organised screening (3 to 5 years); adapted age-group according to European Advisory Group on Cancer Prevention: 25-65 years and according to Austrian 'Vorsorge Neu document': 21-69 years; organisation of pap-smear taking and quality control according to European guideline;

dynamic of HPV-infection. Furthermore, they are needed for calculating life years gained based on age-specific mortality in Austria.

Since these data need to be identified in national statistical data rather than in published literature, they will not be addressed in more detail in this report (for information on the data used in the model in 2007 see the according report [16]).

not covered in this report

9.3 Epidemiological data

The model addresses the impact of different prevention/screening strategies on HPV-infection, on precancerous lesions related to cervical carcinoma and on invasive cervical carcinoma. Hence, data are needed that provide information on the characteristics of the diseases under consideration.

data on characteristics of HPV-infection, precancerous lesions and cervical cancer required

9.3.1 Data on the natural history of the disease

First of all, detailed quantitative and qualitative information on the process of HPV-infection and on the subsequent process of developing persistent infections and finally, precancerous lesions and an invasive carcinoma is required. This includes various types of information, being the time period between infection and precancerous lesions or between lesions and invasive carcinoma, the risk factors for infection and further progression (or regression) of the disease, the transmission patterns of the virus (virus types, risk of transmission per sexual contact etc.), the patterns of natural immunogenicity and the probabilities for transition and regression between the various stages of the disease.

process infection -> cancer includes various types of information

According to chapter 7, parameters that are related to the natural history of a disease may be derived from observational studies/disease registries or from the control group in clinical studies.

observational studies may be relevant source

Because of ethical reasons very few studies exist that have observed the natural history of disease from HPV-infection ->persistent infection ->precancerous lesion ->invasive carcinoma and the possible regression (e.g. infection to clearance of infection). Existing studies are from time periods before screening methods and treatment options became available. For the same ethical reasons, subjects in RCT-control groups will immediately be treated if they develop precancerous lesions. Hence, the progression patterns to invasive carcinoma or the regression to less severe stages are unknown in these women.

because of nature of disease and treatment few such studies available

Not surprisingly, it became apparent that because of the few and quite outdated observational studies that are available the same rare sources are used in a number of published papers and reports on issues related to HPV and cervical cancer. For example the suggested regression/persistence/progression likelihoods of pre-cancerous lesions by Östor [17] are cited by the European Commission guideline on cervical cancer screening [18], by an HTA on Screening [19] or by patient information material on screening and vaccination [20, 21].

same data have been used by many study authors

For efficiency reasons the search for the vast variety of data was restricted to identifying reliable and evidence based overview documents. One document

reliable overview document was identified

that seems to provide extensive and evidence based information is a description of cervical cancer screening that has been developed for patient information purposes and includes data on the natural history of infection and on the development of cervical cancer [20]. Table 10.3-1 gives an overview on the data that are presented in this document.

Table 9.3-1: Information overview on the natural history of disease based on [20]

Time period between infection and invasive carcinoma	15 to 30 years
Time period between infection and precancerous lesion	10 years
Time period between precancerous lesion and invasive carcinoma	> 10 years
Proportion of infected who develop antibodies	50 % to 60 %
Proportion of simultaneous infection with more than one HPV-type	20 % to 30 %
Proportion of infections that clear within 2 years	more than 80 %
Proportion of infections that clear within 3 years	more than 90 %
Proportion of women who develop precancerous lesions after persistent HPV-16 infection after 3 to 5 years	40 %
Risk factors that are associated with precancerous lesions	infection with more than one virus-type, high virusload, immunosuppression, smoking, oral contraceptives
Risk increase in women who take oral contraceptives between age 20 and 30	3.8 to 4.5 times per 1000 women
Percentage of women with CIN 3 or CIS (carcinoma in situ) who develop invasive carcinoma in 5 to 10 years	20 % to 30 %
Regression rate for CIN1 to CIN 3 in 18 to 34 year old women	85 %
Regression rate for CIN 1 to CIN 3 in 'older women'	19 % to 60 %

Additionally, the document presents a table on the regression and progression across different precancerous lesions that is based on several literature sources (see table 10.3-2).

Table 9.3-2: Estimated frequency for regression, persistency and progression between dysplasias without treatment based on different literature sources [20]

Dysplasie-grad	Regression	Persistenz	Progression zu CIN3/CIS*	Progression zu invasivem Ca*
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3 - CIS	32%	56%	–	12% u. mehr**

* Ca = Karzinom, CIN = zervikale intraepitheliale Neoplasie, CIS = Carcinoma in situ.

** Die Angaben variieren zwischen 12%,[21] „weniger als 50%"[24] und 4% bis 70%.[37]

Concerning the HPV transmission patterns, a recent meta-analysis of HPV infection concordance has been identified that may be useful [22]. As for example shown in table 10.3-3, the paper presents the expected and observed HPV concordance (defined as both partners having the HPV outcome of interest).

meta-analysis on HPV infection concordance may be useful for info on transmission patterns

Table 9.3-3: Expected and observed type-specific HPV concordance [22]

	No. of studies	No. of couples	HPV prevalence, *n* (%)		HPV concordance, *n* (%)		OR (95% CI)	I^2
			Females	Males	Expected	Observed		
HPV 6	5	340	49 (14.4)	41 (12.1)	5.9 (1.7)	18 (5.3)	6.60 (0.92-47.50)*	65
HPV 11	5	512	32 (6.3)	21 (4.1)	1.3 (0.3)	7 (1.4)	7.56 (2.63-21.74)†	0
HPV 16	12	1615	479 (29.7)	169 (10.5)	50.1 (3.1)	107 (6.6)	3.42 (2.25-5.20)†	0
HPV 18	6	1464	134 (9.2)	28 (1.9)	2.6 (0.2)	10 (0.7)	7.91 (2.43-25.73)‡	26

NOTE: The table reports unweighted frequencies and percentages along with odds ratios and 95% CIs from random-effects meta-analysis. The table includes only the studies that reported the data required for these calculations.
*$P = 0.06$.
†$P < 0.001$.
‡$P < 0.05$.

Apart from quantitative information, qualitative information on the natural history of disease will be required to better understand the whole disease process. A useful starting point for this type of information is provided by Schiffman et al. [23] and by Bosch et al. [24].

9.3.2 Data on the frequency of HPV infection, precancerous lesions and invasive cervical carcinoma

Data on the epidemiology of HPV-infection and on the occurrence of precancerous lesions and invasive carcinomas including information on the distribution of HPV genotype in those cases in Austria are needed.

Austrian data on HPV infection and epidemiology of its consequences needed

The primary source for this kind of data would be national disease and cancer registries, however, they may not hold detailed enough information. For example, data on the type of precancerous lesion (CIN 1 to CIN 3) or on the associated virus genotype will be needed for the disease model, but the national cancer registry only provides data on the number of newly diagnosed invasive carcinomas and on the number of women who died from cervical carcinoma per year disaggregated by cervical cancer stage. Hence, additional published literature needs to be searched for more detailed information.

national disease/cancer registries provide only limited information

Possible study types from which this kind of information may be extracted include prevalence surveys about the HPV type-specific burden of cervical cancer, population based surveys on the cervical HPV prevalence, specific observational studies in clinical epidemiology such as cohort studies, case-control or cross-sectional studies and randomised controlled trials.

Possible study types: (population based) surveys on HPV prevalence, clinical studies

HPV infection

meta-analysis and Austrian trial analysis on HPV-infection in females

Concerning the prevalence of HPV-infection in females, a meta-analyses on cervical HPV prevalence in 5 continents [25] and an analysis on the Austrian HPV 6, 11, 16 and 18-prevalence among women that participated in a vaccination RCT [26] were available.

data characteristics summarised in table

The data characteristics of these two studies are presented in table 10.3-4. The Austrian study yields only limited information on the overall prevalence of 4 HPV types (against which the quadrivalent vaccination has been developed) in 111 study subjects. The information is further restricted by the fact that prevalence data are from females in young age (16-24 years) only.

no Austrian data in meta-analysis

On the contrary, the meta-analysis on the worldwide HPV-prevalance provides more detailed data on the prevalence of the most frequent HPV-types. Although studies from Western European countries have been included, none of them is from Austria. Furthermore, the age-specific data are presented in a figure without detailed quantitative information on every single age-group. For the latter the reader is referred to online-tables.

Table 9.3-4: Data characteristics in published studies on genotypes in HPV-infection

Study author/year	Six et al. [26]/2008	Bruni et al. [25]/2010
Countries addressed	Austria	5 continents Within Western Europe: Belgium, France, Germany, Switzerland, Netherlands
Age groups analysed	16-24 ; mean: 19.9 (SD: 1.7)	≤ 25 to > 64 years
Race/ethnicity	100% white	Not stated
Genotypes addressed	6, 11, 16, 18	Any HPV type
No of subjects studied	111 (Austrian sample of a European multi-centre RCT)	1,016,719 women with normal cytological findings; Western Europe: 77,445
Results	15 (13.5%) were positive of HPV 6, 11, 16, or 18 Highest prevalence: HPV-16 (11.4 %) HPV-18: 3.5 %	World HPV-prevalence crude: 7.2% (7.1-7.2); adjusted¤: 11.7% (11.6-11.7) Western Europe crude: 7.3% (7.1-7.5); adjusted: 9.0% (8.8 – 9.2) World high-risk crude: 5.5% (5.5-5.6); adjusted: 5.0% (5.0-5.1) Europe most frequent HPV-types: 16: 4.8%; 31: 2.3%; 18: 0.9%; 39: 0.8%; 33, 66: 0.6%; 6: 0.5%; 45, 52, 51, 58: 0.4; 53, 56, 70, 11: 0.3%; 42, 81, 68, 83, 59, 61, 35: 0.2%; 73, 44, 90, 72, 62, 69, 54: 0.1%; Decreasing prevalence over time; highest prevalence in < 25 years, then declining until 54 years and again rising in age ≥55
Comment by study authors	Overall rate of positive HPV-genotype in Austrian sample is lower than in European participants of the trial (25.3 %) in women with normal cytology but similar in those with abnormal cytology	HPV-31 is very common in Europe (2nd rank after HPV-16) but much less in Northern America or Asia; Heterogeneity caused by different HPV-detection methods and by the selection and representativeness of the population is a problem

SD: standard deviation; ¤: standardised by the world's geographical structure; adjusted by geographical region, mean age of women, ending year of study, HPV testing method, proportion of high-risk HPV-types tested, proportion of low-risk HPV types tested, and cluster (analysis of mixtures);

cohort-study on HPV-infection in males

In terms of HPV-infection in males, a cohort-study on the incidence and clearance of genital HPV infection in men in the USA, Brazil and Mexico [27] has recently been published. This type of information on HPV-infection in males has not been available when the LBI-HPV vaccination modelling exercise has been done in 2007.

In the publication, detailed information on the baseline characteristics of the study group and on the results are provided in two tables (see table 10.3-5 on the study results).

data characteristics are presented in table

The results on the incidence per 1000 person months, on the 12-months incidence and on the median time to clearance of an infection include the point estimates as well as the 95% confidence intervals. Further data that are presented in the result table are on the prevalence (absolute and in %), on incident infections, on person months, on new infections and on cleared infections. Furthermore, the study presents 8 Kaplan Meier estimates of the cumulative incidence and time to clearance of any, type 16, oncogenic, and non-oncogenic HPV infections by age.

results only partly generalisable

The authors point out that the results on incidence cannot be generalised to all men in the three countries studied whereas the assessment on factors associated with HPV acquisition and clearance are less prone to bias.

As confirmed by the WHO report on HPV, specific data on the HPV prevalence in males in Austria are not available [28].

Table 9.3-5: Prevalence, incidence and clearance of HPV infection in men [27]

	Prevalence (n=1159)	Incident infections	Person months	Incidence per 1000 person months (95% CI)	12-month Incidence (95% CI)	New infections*	Cleared infections	Median time to clearance (months; 95% CI)
Any HPV	584 (50%)	311	8090	38·4 (34·3–43·0)	39·3% (34·9–43·4)	1572	1038	7·5 (6·8–8·7)
Oncogenic	345 (30%)	311	13 978	22·2 (19·8–24·9)	27·1% (23·8–30·2)	693	465	7·2 (6·7–9·5)
16	75 (6%)	105	23 929	4·4 (3·6–5·3)	6·2% (4·6–7·7)	91	49	12·2 (7·4–20·2)
18	20 (2%)	49	26 090	1·9 (1·4–2·5)	2·4% (1·5–3·4)	44	30	6·3 (6·0–12·7)
31	19 (2%)	35	26 304	1·3 (0·9–1·9)	1·9% (1·1–2·8)	30	22	6·7 (6·4–15·9)
33	2 (<1%)	8	27 087	0·3 (0·1–0·6)	0·5% (0·1–0·9)	8	7	6·4 (6·1–NE)
35	21 (2%)	27	26 337	1·0 (0·7–1·5)	1·3% (0·6–1·9)	24	17	11·6 (8·6–18·1)
39	42 (4%)	65	25 305	2·6 (2·0–3·3)	3·6% (2·4–4·8)	56	37	7·4 (6·2–18·4)
45	13 (1%)	43	26 331	1·6 (1·2–2·2)	2·1% (1·2–2·9)	40	26	6·5 (6·1–18·2)
51	72 (6%)	108	23 753	4·5 (3·7–5·5)	6·4% (4·8–7·9)	96	62	10·3 (6·5,13·8)
52	85 (7%)	104	23 507	4·4 (3·6–5·4)	7·4% (5·7–9·0)	93	68	7·6 (6·3–12·0)
56	24 (2%)	45	25 995	1·7 (1·3–2·3)	1·7% (0·9–2·5)	39	29	6·2 (6·0–11·6)
58	27 (2%)	42	25 945	1·6 (1·2–2·2)	2·8% (1·8–3·8)	38	29	6·7 (6·0–12·0)
59	62 (5%)	95	24 577	3·9 (3·1–4·7)	4·8% (3·5–6·2)	69	46	6·2 (6·1–11·3)
66	58 (5%)	79	24 674	3·2 (2·5–4·0)	4·5% (3·2–5·8)	65	43	6·7 (6·1–16·9)
Non-oncogenic	445 (38%)	313	11 263	27·8 (24·8–31·0)	30·0% (26·3–33·5)	879	573	7·6 (6·8–9·3)
6	77 (7%)	85	23 941	3·6 (2·8–4·4)	4·8% (3·4–6·1)	71	54	6·4 (6·1–10·4)
11	16 (1%)	23	26 608	0·9 (0·5–1·3)	1·0% (0·4–1·6)	17	10	11·8 (6·0–NE)
26	4 (<1%)	9	27 033	0·3 (0·2–0·6)	0·5% (0·1–0·9)	9	5	6·3 (5·9–NE)
40	15 (1%)	18	26 558	0·7 (0·4–1·1)	1·1% (0·4–1·7)	18	10	12·3 (6·1–NE)
42	14 (1%)	34	26 420	1·3 (0·9–1·8)	1·7% (0·9–2·5)	28	14	11·2 (7·9–NE)
53	23 (2%)	49	25 903	1·9 (1·4–2·5)	2·2% (1·3–3·1)	40	22	12·0 (6·5–NE)
54	55 (5%)	84	24 594	3·4 (2·7–4·2)	4·5% (3·2–5·8)	73	51	7·1 (6·0–12·4)
55	31 (3%)	59	25 582	2·3 (1·8–3·0)	3·7% (2·5–4·8)	52	32	11·3 (6·6–17)
61	59 (5%)	65	24 754	2·6 (2·0–3·3)	4·1% (2·8–5·3)	59	42	6·2 (6·0–9·3)
62	85 (7%)	87	23 721	3·7 (2·9–4·5)	6·2% (4·6–7·7)	79	49	12·2 (7·9–17·1)
64	1 (<1%)	4	27 213	0·1 (0·0–0·4)	0·3% (0–0·6)	4	3	6·5 (5·5–NE)
67	4 (<1%)	22	26 997	0·8 (0·5–1·2)	0·8% (0·2–1·3)	16	14	6·0 (5·8–11·7)
68	31 (3%)	55	25 741	2·1 (1·6–2·8)	2·5% (1·6–3·5)	43	35	6·3 (6·0–7·7)
69	3 (<1%)	4	27 182	0·1 (0·0–0·4)	0·1% (0·0–0·3)	4	3	5·8 (5·5–NE)
70	26 (2%)	33	25 981	1·3 (0·9–1·8)	2·1% (1·2–3·0)	30	18	12·0 (6·2–NE)
71	13 (1%)	17	26 743	0·6 (0·4–1·0)	1·2% (0·5–1·8)	17	11	12·1 (6·8–NE)
72	14 (1%)	31	26 466	1·2 (0·8–1·7)	1·8% (1·0–2·6)	27	16	6·2 (6·1–NE)
73	15 (1%)	21	26 525	0·8 (0·5–1·2)	1·2% (0·5–1·9)	20	15	6·4 (6·1–NE)
81	42 (4%)	50	25 404	2·0 (1·5–2·6)	3·0% (1·9–4·0)	46	31	6·4 (6·2–10·0)
82	8 (<1%)	16	26 827	0·6 (0·3–1·0)	1·0% (0·4–1·7)	12	9	7·4 (6·2–NE)
83	34 (3%)	30	26 065	1·2 (0·8–1·6)	1·8% (1·0–2·7)	24	21	6·3 (5·9–11·5)
84	88 (8%)	116	23 336	5·0 (4·1–6·0)	6·7% (5·1–8·3)	98	61	11·2 (6·6–16·6)
CP6108	66 (6%)	98	24 160	4·1 (3·3–4·9)	5·3% (3·9–6·7)	84	43	12·1 (9·0–NE)
IS39	5 (<1%)	9	27 057	0·3 (0·2–0·6)	0·3% (0·0–0·6)	8	4	19·8 (5·9–NE)

Data are number or number (%), unless otherwise indicated. NE=not estimable. *Number of new infections was larger than incident infections because multiple infections were judged individually in the clearance analysis; new infections detected at a participant's last visit were not analysed for clearance.

Table 2: **Prevalence at enrolment, and incidence and clearance of human papillomavirus (HPV) infections in men**

Precancerous lesions and cervical cancer

some published sources on cancer epidemiology available

In addition to national or regional cancer registries, data on the Austrian cervical cancer epidemiology can also be identified in published literature. Although these data are again from cancer registries or from other secondary sources (e.g. from the WHO database) they may yield additional and more detailed information that is not directly accessible from registries. One data source is a WHO report on HPV and cervical cancer in Austria [28].

Incidence

Austrian incidence data

The report contains information on cervical cancer incidence in Austria compared to Europe and the world (see table 10.3-6) as well as comparative data on the incidence of cervical cancer disaggregated by Austrian cancer registry (see table 10.3-7). Furthermore, age-standardised rates on cervical cancer by histological type across the different registries and the annual number of new cancer cases by age-group are provided in the report (see table 10.3-8 and figure 10.3-1). Data on precancerous lesions are not available.

Table 9.3-6: Incidence of cervical cancer in Austria, Western Europe and the world [28]

Indicator	Austria	Western Europe	World
Crude incidence rate[1]	11.0	9.7	15.8
Age-standardized incidence rate[1]	7.8	6.9	15.3
Cumulative risk (%). Ages 0-74 years[1]	0.7	0.6	1.6
Annual number of new cancer cases	472	9318	529828

Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. (Specific methodology for Austria: National incidence rates (1990-2004) projected to 2008 and applied to the national population (2008), except prostate cancer (C61): incidence rates (2000-2004) were applied to 2008 population. For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=040.)

Table 9.3-7: Incidence of cervical cancer in Austria by cancer registry [28]

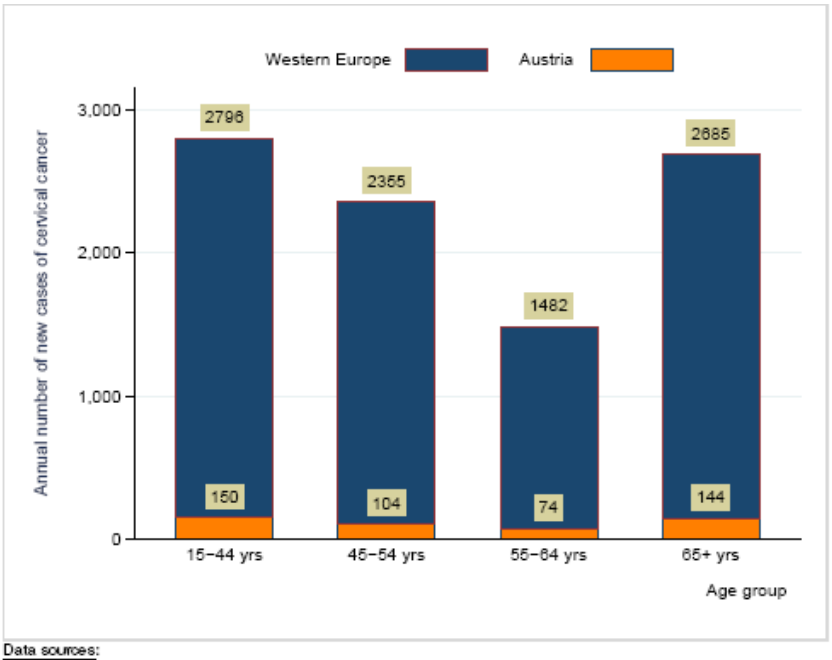
Cancer registry	Period	N cases[1]	Crude rate[2]	ASR[2]
National	1998-2002	2644	12.8	8.7
Tyrol	1998-2002	285	16.6	12.0
Vorarlberg	1998-2002	82	9.3	6.8

ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Accumulated number of cases during the period
[2] Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Table 9.3-8: Age-standardised incidence rates of cervical cancer by histological type and cancer registry in Austria [28]

		Carcinoma			
Cancer registry	Period	Squamous	Adeno	Other	Unspec.
National	1998-2002	6.3	0.9	0.2	0.9
Tyrol	1998-2002	9.9	1.3	0.3	0.3
Vorarlberg	1998-2002	4.6	1.3	0.2	0.5

Standardized rates have been estimated using the direct method and the World population as the reference.
Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 9.3-1: Annual number of new cases of cervical cancer by age-group [28]

Mortality

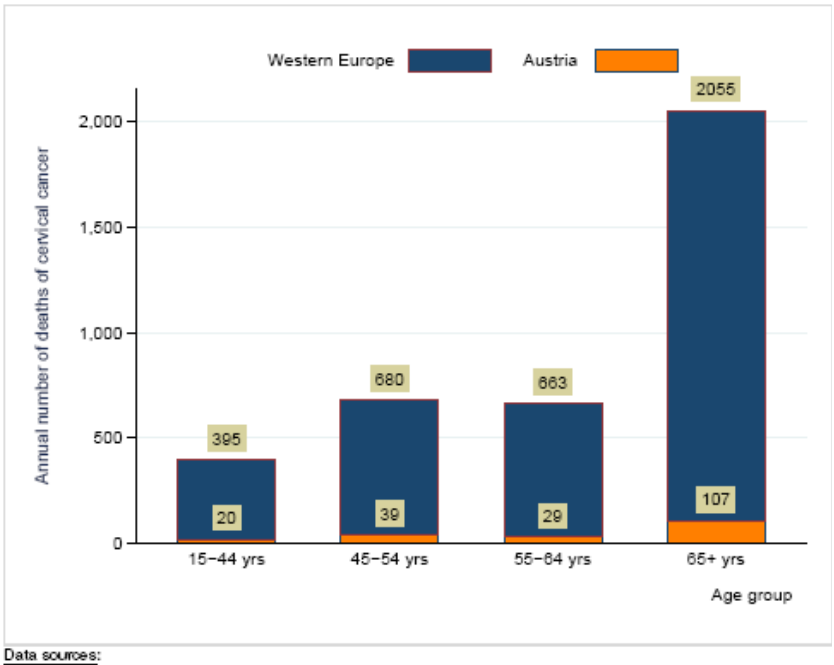
Austrian mortality data

The same WHO report contains data on cervical cancer mortality in Austria, compared to Western Europe and the world and on the number of cervical cancer deaths by age-group in Austria (see table 10.3-9 and figure 10.3-2).

Table 9.3-9: Mortality of cervical cancer in Austria, Western Europe and the world [28]

Indicator	Austria	Western Europe	World
Crude mortality rate[1]	4.6	4.0	8.2
Age-standardized mortality rate[1]	2.3	2.0	7.8
Cumulative risk (%) ages 0-74 years[1]	0.2	0.2	0.9
Annual number of deaths	195	3794	275128

Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. (Specific methodology for Austria: Recorded national mortality for 2008 (source WHO Mortality Data). For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=040.)



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 9.3-2: Annual number of cervical cancer deaths by age-group [28]

9.3.3 Data on HPV genotypes in HPV infection, precancerous lesions and invasive cancer cases

The frequency of HPV genotypes in HPV infection has already been described in the studies that analysed HPV infection (see chapter 10.3.2). Details are provided by Six et al. [26] for Austria, Bruni et al. [25] for the world regions and Giulinao et al. [27] for males.

small study on HPV-types in adenocarcinomas in situ

A recent study presents the HPV-type distribution in adenocarcinomas in situ that was observed in two phase 3 clinical trials of the quadrivalent vaccine 'Gardasil' [29]. Most of the women in the small sample analysed were from Europe (77% out of 22 subjects) and of white ethnicity. The study provides a table on the HPV DNA detected in AIS (adenocarcinoma in situ) lesions for every study subject analysed. The authors do, however, not present a summary table or a written summary on the overall HPV type distribution in AIS lesions. Only in the discussion, the authors mention that 96% of all AIS lesions were positive to HPV 16 or 18.

It may be of use for the planned HPV-model that the paper contains a table on the time to detection of AIS, stratified by day 1 HPV DNA status and pap smear result.

limited validity

However, since the data are from a RCT study population, their validity is limited to persons with the demographic characteristics of the study population (e.g. mean age of 20.4 years).

two large studies on HPV genotype distribution in invasive cervical cancer

Concerning HPV genotype attribution in invasive cervical cancer, a recent retrospective cross-sectional study on the worldwide HPV genotype attribution [30] and a meta-analyses on published literature have been identified [31].

analysis of archived specimens in 38 countries and…

In the former, paraffin-embedded specimens from cases (aged 16-97 years) with cervical cancer were obtained from hospital archives in 38 countries including 10 European countries (with 2058 specimens). Austria was not part of the study. Table 10.3-10 and table 10.3-11 demonstrate the type of data that are presented in the study. These include the prevalence of 33 HPV genotypes analysed by region and histological type of cervical cancer. A third table yields information on the number and percentage of overall HPV positive cases, single HPV types and multiple HPV types by region. The authors refer to a web appendix that contains additional information, for example on the mean age of diagnosis.

Table 9.3-10: HPV genotypes in invasive cancer cases by region [30]

	Total (n=8977)	Europe (n=2058)	North America (n=160)	Central South America (n=3404)	Africa (n=544)	Asia (n=2641)	Oceania (n=170)
HPV 6	10 (<1%)	3 (<1%)	..	3 (<1%)	..	1 (<1%)	3 (2%)
HPV 11	2 (<1%)	..	..	1 (<1%)	..	1 (<1%)	..
HPV 16	5439 (61%)	1348 (66%)	115 (72%)	2015 (59%)	259 (48%)	1597 (60%)	100 (59%)
HPV 18	918 (10%)	150 (7%)	11 (7%)	309 (9%)	123 (23%)	295 (11%)	34 (20%)
HPV 26	31 (<1%)	3 (<1%)	..	17 (<1%)	..	11 (<1%)	..
HPV 30	31 (<1%)	5 (<1%)	..	14 (<1%)	3 (<1%)	9 (<1%)	..
HPV 31	335 (4%)	69 (3%)	5 (3%)	166 (5%)	10 (2%)	80 (3%)	1 (<1%)
HPV 33	345 (4%)	117 (6%)	5 (3%)	119 (3%)	8 (1%)	92 (3%)	3 (2%)
HPV 34	6 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	..	1 (<1%)	..
HPV 35	175 (2%)	46 (2%)	..	72 (2%)	27 (5%)	27 (1%)	4 (2%)
HPV 39	143 (2%)	27 (1%)	2 (1%)	76 (2%)	3 (<1%)	31 (1%)	3 (2%)
HPV 39*	3 (<1%)	1 (<1%)	..	1 (<1%)	1 (<1%)	..	..
HPV 42	3 (<1%)	3 (<1%)	..	..	..	..	..
HPV 44	1 (<1%)	1 (<1%)	..	..	..	..	..
HPV 45	528 (6%)	80 (4%)	9 (6%)	230 (7%)	54 (10%)	146 (6%)	9 (5%)
HPV 51	114 (1%)	28 (1%)	2 (1%)	53 (2%)	13 (2%)	19 (<1%)	..
HPV 52	253 (3%)	40 (2%)	5 (3%)	91 (3%)	14 (3%)	101 (4%)	1 (<1%)
HPV 53	24 (<1%)	10 (<1%)	1 (<1%)	9 (<1%)	..	1 (<1%)	3 (2%)
HPV 56	75 (<1%)	32 (2%)	1 (<1%)	20 (<1%)	4 (<1%)	18 (<1%)	..
HPV 58	203 (2%)	27 (1%)	3 (2%)	67 (2%)	4 (<1%)	102 (4%)	..
HPV 59	95 (1%)	15 (<1%)	..	42 (1%)	1 (<1%)	36 (1%)	..
HPV 61	1 (<1%)	..	..	1 (<1%)	..	..	..
HPV 66	7 (<1%)	2 (<1%)	..	2 (<1%)	2 (<1%)	1 (<1%)	..
HPV 67	26 (<1%)	3 (<1%)	..	13 (<1%)	..	10 (<1%)	..
HPV 68	59 (<1%)	13 (<1%)	..	20 (<1%)	1 (<1%)	25 (<1%)	..
HPV 68†	31 (<1%)	4 (<1%)	..	17 (<1%)	1 (<1%)	3 (<1%)	6 (4%)
HPV 69	7 (<1%)	..	..	6 (<1%)	1 (<1%)	..	..
HPV 70	9 (<1%)	1 (<1%)	..	3 (<1%)	..	5 (<1%)	..
HPV 73	43 (<1%)	16 (<1%)	..	14 (<1%)	1 (<1%)	12 (<1%)	..
HPV 74‡	2 (<1%)	..	..	..	..	1 (<1%)	..
HPV 82	6 (<1%)	..	..	4 (<1%)	..	2 (<1%)	..
HPV 91	1 (<1%)	1 (<1%)	..	..	..	..	..
HPV undetermined	52 (<1%)	10 (<1%)	0	15 (<1%)	13 (2%)	12 (<1%)	2 (1%)

Data are number (%) and are based on the upper estimate attribution of multiple HPV types. *HPV type 39, 68, or 73. †HPV type 68 or 73. ‡One case in the total attributable to infection with multiple HPV types, and no case with exclusively HPV 74.

Table 2: **Human papillomavirus (HPV) genotypes in cases of invasive cervical cancer that were positive for HPV DNA, by region**

Table 9.3-11: HPV genotypes in invasive cancer cases, by histological diagnosis [30]

	Total (n=8977)	Squamous cell carcinoma (n=8252)	Adenocarcinoma (n=470)	Adenosquamous cell carcinoma (n=155)	Other* (n=100)
HPV 6	10 (<1%)	9 (<1%)	1 (<1%)	..	..
HPV 11	2 (<1%)	2 (<1%)	..	..	..
HPV 16	5439 (61%)	5090 (62%)	235 (50%)	61 (39%)	51 (51%)
HPV 18	918 (10%)	687 (8%)	152 (32%)	49 (32%)	30 (30%)
HPV 26	31 (<1%)	31 (<1%)	..	..	..
HPV 30	31 (<1%)	30 (<1%)	1 (<1%)	..	..
HPV 31	335 (4%)	328 (4%)	3 (<1%)	3 (2%)	1 (1%)
HPV 33	345 (4%)	338 (4%)	2 (<1%)	4 (3%)	1 (1%)
HPV 34	6 (<1%)	6 (<1%)	..	..	..
HPV 35	175 (2%)	169 (2%)	2 (<1%)	2 (1%)	2 (2%)
HPV 39	143 (2%)	134 (2%)	1 (<1%)	4 (3%)	3 (3%)
HPV 39†	3 (<1%)	3 (<1%)	..	..	..
HPV 42	3 (<1%)	3 (<1%)	..	..	..
HPV 44	1 (<1%)	1 (<1%)	..	..	..
HPV 45	528 (6%)	446 (5%)	56 (12%)	18 (12%)	9 (9%)
HPV 51	114 (1%)	108 (1%)	3 (<1%)	1 (<1%)	1 (1%)
HPV 52	253 (3%)	252 (3%)	..	1 (<1%)	..
HPV 53	24 (<1%)	23 (<1%)	1 (<1%)	..	..
HPV 56	75 (<1%)	72 (<1%)	2 (<1%)	..	1 (1%)
HPV 58	203 (2%)	199 (2%)	..	3 (2%)	1 (1%)
HPV 59	95 (1%)	90 (1%)	3 (<1%)	2 (1%)	..
HPV 61	1 (<1%)	1 (<1%)	..	..	..
HPV 66	7 (<1%)	6 (<1%)	..	1 (<1%)	..
HPV 67	26 (<1%)	26 (<1%)	..	..	..
HPV 68	59 (<1%)	57 (<1%)	1 (<1%)	1 (<1%)	..
HPV 68‡	31 (<1%)	28 (<1%)	2 (<1%)	1 (<1%)	..
HPV 69	7 (<1%)	7 (<1%)	..	..	..
HPV 70	9 (<1%)	9 (<1%)	..	..	..
HPV 73	43 (<1%)	43 (<1%)	..	..	..
HPV 74	2 (<1%)	2 (<1%)	..	..	..
HPV 82	6 (<1%)	6 (<1%)	..	..	..
HPV 91	1 (<1%)	1 (<1%)	..	..	..
HPV undetermined	52 (<1%)	44 (<1%)	5 (1%)	3 (2%)	0

Data are number (%). *Includes undifferentiated, neuroendocrine, not otherwise specified, basal adenoid, and cystic adenoid carcinomas. †HPV type 39, 68, or 73. ‡HPV type 68 or 73.

Table 3: Human papillomavirus (HPV) genotypes in cases of invasive cervical cancer that were positive for HPV DNA, by histological diagnosis

…meta analysis of published studies

The meta-analysis [31] includes 243 studies covering a total of 30,848 cases of invasive cervical cancer. 79 studies with 9,015 cases were from Europe including Austria. The data in the publication yield information on the HPV types (overall, by histological type and by year of publication), on the HPV-16 prevalence in invasive cervical cancer across strata of regions and on the ten most frequently detected HPV types from 1990 to 2010 by region. The latter, however, is presented in figures without detailed numerical information. The limitations of the data are that the changing prevalence over time may also be due to changes in the sensitivity of the detection methods and the increasing prevalence of multiple infections complicates the estimation of proportions of cancer that can be attributable to groups of HPV types.

Additionally, the WHO-report on HPV and related cancers provides summary information on HPV-genotypes in Austria. However, the data are restricted to the distribution of HPV-genotypes in invasive cervical cancer (see table 10.3-12 and figure 10.3-3). Data on the distribution of HPV-genotypes in precancerous lesions are not available. To a great extent the data in the report are derived from the same sources as mentioned in the earlier paragraphs.

some data also in WHO report

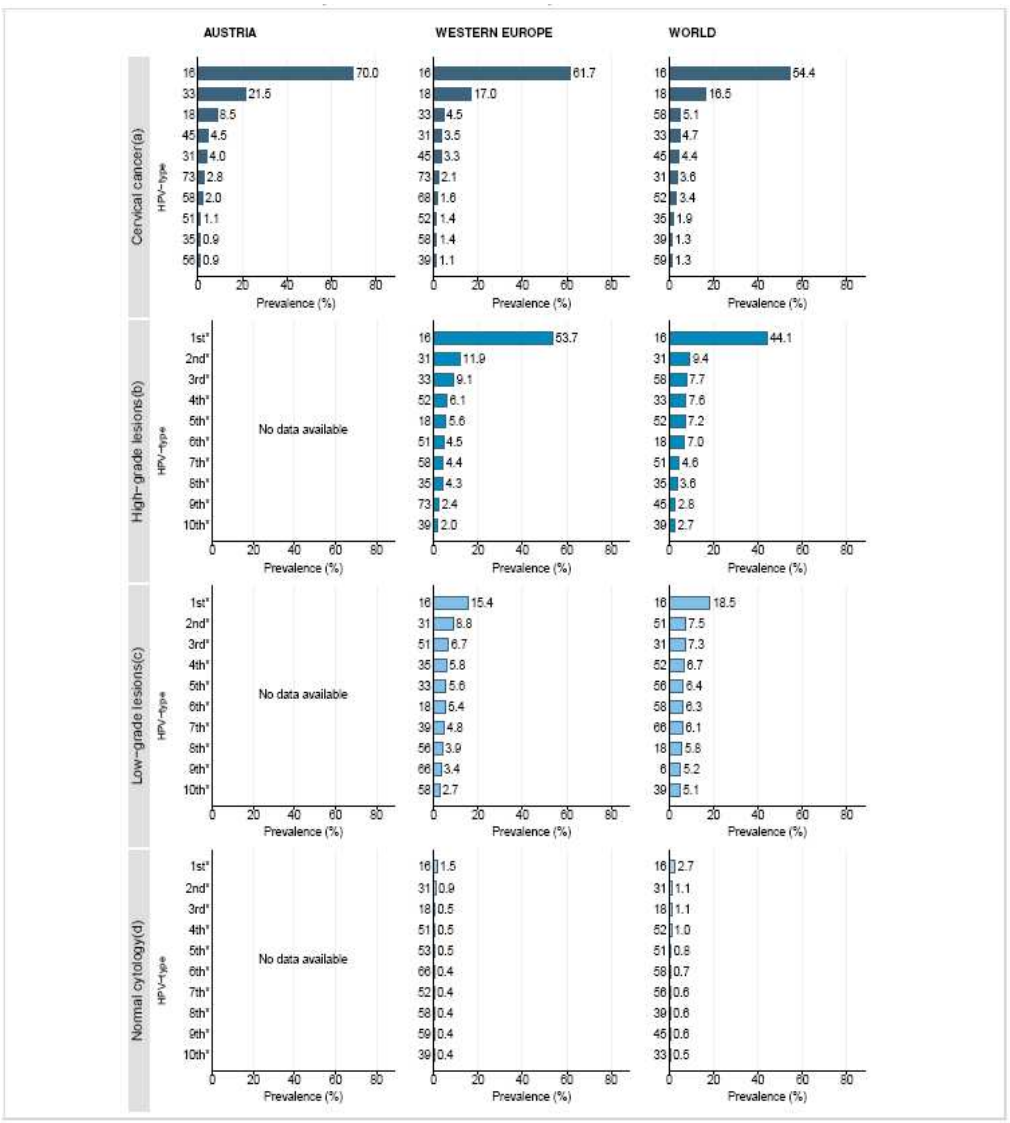
Table 9.3-12: Prevalence of HPV-16 and HPV-18 by cytology in Austria, Western Europe and the world [28]

	Austria		Western Europe		World	
	No. tested	HPV 16/18 Prevalence % (95% CI)	No. tested	HPV 16/18 Prevalence % (95%CI)	No. tested	HPV 16/18 Prevalence % (95%CI)
Normal cytology[a]	-	- -	46795	2.0 (1.9-2.1)	218339	3.8 (3.7-3.9)
Low-grade lesions†[b]	-	- -	1276	20.8 (18.6-23.1)	14762	24.3 (23.6-25.0)
High-grade lesions‡[c]	-	- -	2422	59.3 (57.3-61.3)	14901	51.1 (50.3-51.9)
Cervical cancer[d]	200	78.5 (72.2-84.0)	2352	78.7 (77.0-80.3)	22826	70.9 (70.3-71.5)

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
Abbreviations used:
95% CI: 95% Confidence Interval
†Low-grade lesions: LSIL or CIN-1
‡High-grade lesions: CIN-2, CIN-3, CIS or HSIL
Data sources:
[a] Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007;7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).
[b] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford GM, Cancer Epidemiol Biomarkers Prev 2005; 14: 1157
[c] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;89:101 | Smith JS Int J Cancer 2007;121:621
[d] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2008; 122: 1684
Specific for Austria: Bachtiary B, Int J Cancer 2002; 102: 237 | Widschwendter A, Cancer Lett 2003; 202: 231

For Western Europe and the World, refer to specific reports or methods document for complete data sources.

Figure 9.3-3: Ten most frequent HPV-types among women with and without cervical lesions in Austria compared to Western Europe and the World [28]



The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
*No data available. No more types than shown were tested or were positive

The ranking of the ten most frequent HPV types may present less than ten types because only a limited number of types were tested or were HPV-positive.

Data sources:
[a] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2006; 122: 1684
Specific for Austria: Bachtiary B, Int J Cancer 2002; 102: 237 | Widschwendter A, Cancer Lett 2003; 202: 231
[b] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;89:101 | Smith JS Int J Cancer 2007;121:621
[c] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford GM, Cancer Epidemiol Biomarkers Prev 2005; 14: 1157
[d] Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007; 7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).

For Western Europe and the World, refer to specific reports or methods document for complete data sources.

9.4 Data on the interventions compared

9.4.1 Screening

Data on screening can be categorised into data on general Austrian screening characteristics, data on state of the art of providing the screening (recommended intervals, age groups, quality assurance methods, organisational issues) and data on test accuracy.

screening data: Austrian characteristics, state of the art, test accuracy

Characteristics of Screening in Austria

Information on characteristics of screening (e.g. participation rates) are available from routine data which are beyond the scope of the report. Additionally, published data on the Austrian characteristics are available in the WHO report on HPV [28]. These include main characteristics (screening ages, intervals etc.) (see table 10.4-1), general coverage (table 10.4-2), and coverage by age (figure 10.4-1). Furthermore, the report presents coverage by Austrian regions.

characteristics of screening in Austria from routine data and WHO report

Table 9.4-1: Main characteristics of cervical cancer screening in Austria [28]

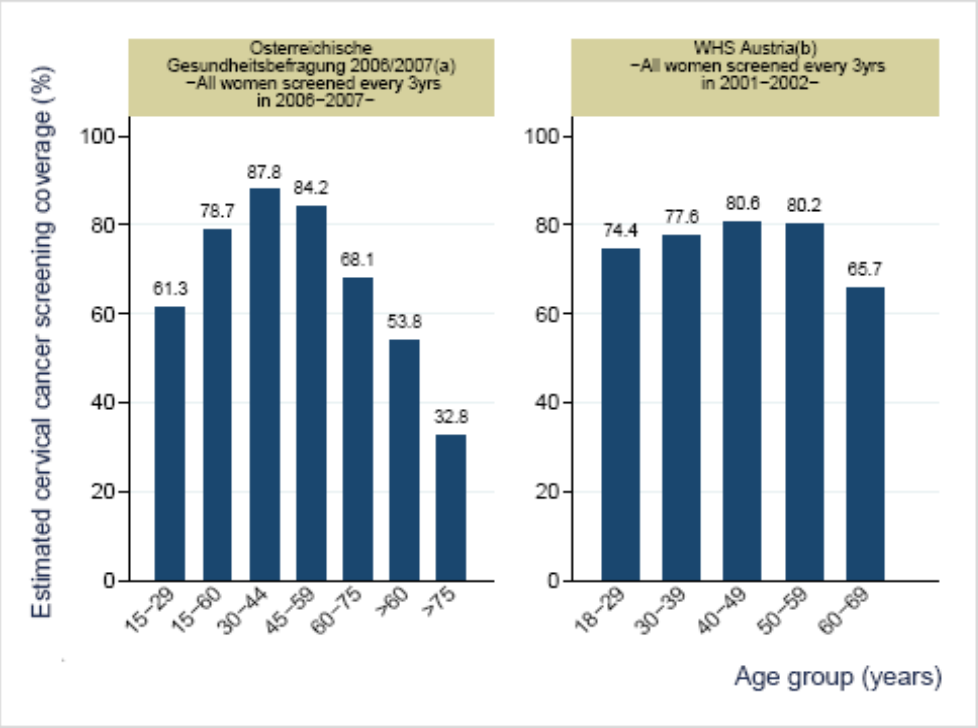
Indicator	Value
Screening ages (years)	>=20
Screening interval (years) or frequency of screens	Annual
Lifetime number of recommended smears	50 (up to age 70)
Smear taker	Gynaecologists

Variable screening ages and screening intervals or frequency of screens depend on different guidelines followed in the country.
Data sources:
IARC Handbooks of Cancer Prevention Vol. 10: Cervix Cancer Screening. IARC Press. Lyon, 2005.

Table 9.4-2: Estimated coverage of cervical cancer screening in Austria [28]

Reference	Year	Population studied	Rural or Urban	N Women	Age range	Coverage (%)	Within the last year(s)
Osterreichische Gesundheitsbefragung 2006/2007[a]	2006-2007	General female population	All	3624300	>15	80.9	Ever
			All	3624300	>15	71.5	3y
WHS Austria[b]	2001-2002	General female population	All	658	18-69	75.9	3y
			Urban	475	18-69	75.9	3y
			Rural	183	18-69	76.0	3y

Notes and sources:
[a] Austrian Health Interview. Population-based survey of approximately 15000 inhabitants and extrapolation to the population.
Österreichische Gesundheitsbefragung 2006/2007 - Austrian Health Interview Survey. Vienna, Austria: Bundesministerium für Gesundheit, Familie und Jugend; 2007.
[b] WHO Household Surveys with multistage cluster sampling. Screening coverage among women aged 18-69.
World Health Surveys. Geneva: World Health Organization (WHO); 2003.



Notes and sources:
[a] Austrian Health Interview. Population-based survey of approximately 15000 inhabitants and extrapolation to the population.
Österreichische Gesundheitsbefragung 2006/2007 - Austrian Health Interview Survey. Vienna, Austria: Bundesministerium für Gesundheit, Familie und Jugend; 2007.
[b] WHO Household Surveys with multistage cluster sampling. Screening coverage among women aged 18-69. World Health Surveys. Geneva: World Health Organization (WHO); 2003.

Figure 9.4-1: Estimated coverage of cervical cancer screening in Austria, by age and study [28]

State of the art in screening provision (interval, quality assurance)

EU guideline for information on state of the art in screening

Guidelines have been identified as the primary data source for state of the art information on screening programmes. For the state of the art in cervical cancer screening an evidence based supranational guideline by the European Union has been identified as most relevant [18].

state of the art is variable, document shows impact from different strategies

Generally, no overall standard exists in terms of screening intervals and starting/ending age, while there is a clear recommendation in favour of an organised screening in contrast to an opportunistic screening. The documents provide various tables that demonstrate the % reduction in cumulative incidence of cancer depending on different screening intervals, age groups screened and coverage rates (see table 10.4-3 for an example)

Table 9.4-3: Reduction in cumulative incidence of squamous cell carcinoma of the cervix uteri with different screening intervals and coverage rates (aged 35-64) in comparison to expectations without screening [18]

Screening interval	Proportion of screened	% Reduction in cumulative incidence	Number of tests per woman
1 year	20%	19	6
2 year	30%	28	4.5
3 years	40%	37	4
5 years	50%	42	3
10 years	80%	51	2.4

Additionally, some information on recommendations for Austria can be found in the document on 'Vorsorge Neu' [32].

Test accuracy of the Papanicolaou Test (Pap-test)

data on test accuracy from recent HTA report

According to the recommendations in chapters 5 and 7, the primary sources for test-accuracy data are RCTs and meta-analyses. A recent HTA report on HPV-DNA testing in cervical carcinoma screening [33] provides an overview-table on the sensitivity and specificity of Pap-smears related to CIN 1 to CIN 3 and invasive carcinoma derived from a number of meta-analyses (see table 10.4-4).

Table 9.4-4: Sensitivity and specificity of HPV-DNA and Pap-Screening for CIN 1, CIN 2, CIN 3 and invasive carcinoma [33]

Screeningtest	Zielgröße	Schwellen-wert	Sensiti-vität (%)	95 %-KI	Spezi-fität (%)	95 %-KI	Quelle
HPV (HC2)	Keine CIN	1 pg/ml	---	---	91,7	90,3-93,1	23
HPV (HC2)	CIN 1 und höher	1 pg/ml	80,6	76,3-84,3	---	---	25
HPV (HC2)	CIN 2 und höher	1 pg/ml	98,1	96,8-99,4	---	---	23
HPV (HC2)	CIN 3 und höher	1 pg/ml	98,1	96,8-99,4	---	---	23
Pap	Keine CIN	(LSIL+)	---	---	95,0	94,5-96,4	67,83
Pap	CIN 1 und höher	(LSIL+)	47,1	44,8-49,4	---	---	67,83
Pap	CIN 2 und höher	(LSIL+)	71,8	67,0-76,2	---	---	67,83
Pap	CIN 3 und höher	(LSIL+)	71,8	67,0-76,2	---	---	67,83
HPV (HC2) + Pap	Keine CIN	1 pg/ml und (ASC-US+)	---	---	87,3	84,2-90,4	6
HPV (HC2) + Pap	CIN 1 und höher	1 pg/ml und (ASC-US+)	81,5	76,8-84,8	---	---	6
HPV (HC2) + Pap	CIN 2 und höher	1 pg/ml und (ASC-US+)	99,2	97,4-100,0	---	---	6
HPV (HC2) + Pap	CIN 3+ und höher	1 pg/ml und (ASC-US+)	99,2	97,4-100,0	---	---	6

ASC-US = Atypical squamous cells of undetermined significance. CIN = Zervikale intraepitheliale Neoplasie. DNA = Desoxyribo-nukleinsäure. HC = Hybrid Capture. HPV = Humanes Papillomavirus. KI = Konfidenzintervall. LSIL = Low-grade squamous intraepithelial lesion. Pap = Test nach Papanicolaou.

Furthermore, the report contains a table derived from another secondary source on the likelihoods for the Pap-test of obtaining a specific test result dependent on different health states.

Table 9.4-5: Likelihood to obtain a specific test result dependent on different health states [33]

Wahrer Gesundheitszustand	Zytologischer Befund	Wahrscheinlichkeit
Keine Läsion	ASC-US (Pap IIw)	0,525
Keine Läsion	LSIL (Pap III, IIID)	0,384
Keine Läsion	HSIL (Pap III, IIID, IV)	0,088
Keine Läsion	Karzinom (Pap V)	0,0028
CIN 1	ASC-US (Pap IIw)	0,233
CIN 1	LSIL (Pap III, IIID)	0,688
CIN 1	HSIL (Pap III, IIID, IV)	0,078
CIN 1	Karzinom (Pap V)	0,0015
CIN 2, CIN 3	ASC-US (Pap IIw)	0,097
CIN 2, CIN 3	LSIL (Pap III, IIID)	0,307
CIN 2, CIN 3	HSIL (Pap III, IIID, IV)	0,586
CIN 2, CIN 3	Karzinom (Pap V)	0,010
Karzinom (FIGO I bis FIGO IV)	ASC-US (Pap IIw)	0,116
Karzinom (FIGO I bis FIGO IV)	LSIL (Pap III, IIID)	0,071
Karzinom (FIGO I bis FIGO IV)	HSIL (Pap III, IIID, IV)	0,210
Karzinom (FIGO I bis FIGO IV)	Karzinom (Pap V)	0,604

ASC-US = Atypical squamous cells of undetermined significance. CIN = Zervikale intraepitheliale Neoplasie. FIGO = Karzinomstadium nach Klassifikation der Fédération Internationale de Gynécologie et d'Obstétrique. HSIL = High-grade intraepithelial lesion. LSIL = Low-grade intraepithelial lesion

Test accuracy of follow-up diagnostic tests

HTA report provides data on test accuracy of colposcopy

The HTA on HPV-DNA testing additionally presents results from a meta-analysis on the sensitivity and specificity of colposcopy, being 96% and 48% respectively [33].

9.4.2 HPV vaccination

Efficacy

According to the standards in the manuals (chapter 5 and 7), vaccine efficacy data need to be based on high-level evidence, namely RCTs or meta-analyses.

many RCTs on vaccine efficacy available since 1998

Starting already in 1998, a number of RCTs have been undertaken for both, the bivalent and quadrivalent vaccine. Publications are available for different study endpoints (e.g. immunogenicity, persistent genotype-specific HPV infection, HPV-genotype specific precancerous lesions) and target populations (e.g. 15-24 year old females, 18-45 year old females, 16-26 year old males). So far, younger age groups from 9 to 14 years that are the primary target group for the vaccine have not been included in RCTs that analysed the relevant endpoints (such as precancerous lesions or HPV infection).

RCTs on the efficacy and safety of the vaccines against cervical HPV infection and diseases among females have been published by Koutsky et al. [34], Mao et al. [35], Harper et al. [36, 37], Villa et al. [38, 39], by the 'FUTURE I Study Group' and the 'FUTURE II study group' on the quadrivalent vaccine (Garland et al. [40], Brown et al. [41], Wheeler et al. [42], Future II Study group [43]), by the 'PATRICIA-trial group' on the bivalent vaccine (Paavonen et al. [44, 45]), by Munoz et al. [46], by De Carvalho et al. [47] and by Castellsague et al. [48].

typical information in RCTs: persistent infection, CIN

several types of analysis

The data that are typically provided in the studies include vaccine efficacy against 6/12-months persistent infection and against cervical intraepithelial neoplasia (CIN) grade 1, 2 or more (CIN 2+, CIN 3+) that are associated with HPV types 16 and 18. The studies usually distinguish between sero- or DNA-negative females and those that had already been infected. Additionally, in-

tention-to-treat and/or per-protocol-analysis study results are presented (see table 10.4-6for data example). Usually, data on the cumulative incidence of certain outcome parameters are included in the papers. Finally, safety outcomes are presented.

Table 9.4-6: End-of-study efficacy against the combined incidence of vaccine type-related infection of 6 months duration, CIN or EGL [48]

	HPV 6/11/16/18-related outcomes				HPV 16/18-related outcomes			
	n(m)				*n(m)*			
Analysis population end point	qHPV	Placebo	Observed efficacy	95% CI	qHPV	Placebo	Observed efficacy	95% CI
Per-protocol efficacy population (PPE)								
Overall persistent infection, CIN, or EGL	10 (4)	86 (41)	88.7	(78.1, 94.8)	8 (4)	51 (23)	84.7	(67.5, 93.7)
24–34-year-olds	5 (2)	56 (24)	91.3	(78.4, 97.3)	5 (2)	35 (13)	86.0	(64.0, 95.7)
35–45-year-olds	5 (2)	30 (17)	83.8	(57.9, 95.1)	3 (2)	16 (10)	81.8	(36.3, 96.6)
By end point								
Persistent infection	9 (2)	85 (39)	89.6	(79.3, 95.4)	7 (2)	50 (21)	86.2	(69.4, 94.7)
CIN (any grade)	1 (1)	17 (9)	94.1	(62.5, 99.9)	1 (1)	13 (7)	92.4	(49.1, 99.8)
CIN 2/3 or worse	1 (1)	6 (4)	83.3	(−37.6, 99.6)	1 (1)	6 (4)	83.4	(−36.7, 99.6)
EGL	0 (0)	7 (4)	100	(30.8, 100)	0 (0)	0 (0)	NA	NA
Condyloma	0 (0)	7 (4)	100	(30.8, 100)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	NA	NA
HPV-naive to the relevant type population (NRT)								
Overall persistent infection, CIN, or EGL	27 (20)	130 (77)	79.9	(69.4, 87.3)	19 (14)	85 (48)	78.3	(64.0, 87.5)
24–34-year-olds	15 (11)	90 (54)	83.7	(71.7, 91.3)	13 (9)	60 (33)	78.7	(60.7, 89.2)
35–45-year-olds	12 (9)	40 (23)	71.3	(44.1, 86.3)	6 (5)	25 (15)	78.0	(42.6, 92.3)
By end point								
Persistent infection	26 (19)	129 (76)	80.4	(69.9, 87.7)	18 (13)	84 (47)	79.1	(64.9, 88.2)
CIN (any grade)	3 (3)	27 (16)	89.0	(64.1, 97.9)	3 (3)	21 (12)	85.9	(52.7, 97.3)
CIN 2/3 or worse	3 (3)	8 (4)	62.7	(−55.5, 93.6)	3 (3)	8 (4)	62.9	(−54.6, 93.7)
EGL	2 (1)	11 (8)	81.9	(17.2, 98.1)	1 (1)	0 (0)	NA	NA
Condyloma	1 (0)	11 (8)	91.0	(37.9, 99.8)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	NA	NA
Intention-to-treat population (ITT)								
Overall persistent infection, CIN, or EGL	116 (108)	214 (154)	47.2	(33.5, 58.2)	95 (90)	160 (115)	41.6	(24.3, 55.2)
24–34-year-olds	75 (71)	134 (94)	44.1	(25.3, 58.5)	60 (57)	100 (70)	39.4	(16.0, 56.9)
35–45-year-olds	41 (37)	80 (60)	51.2	(28.0, 67.3)	35 (33)	60 (45)	43.9	(13.4, 64.1)
By end point								
Persistent infection	110 (102)	211 (151)	49.0	(35.5, 59.9)	91 (86)	157 (112)	42.8	(25.5, 56.3)
CIN (any grade)	29 (25)	55 (41)	47.5	(16.3, 67.7)	28 (24)	48 (36)	41.9	(5.6, 64.9)
CIN 2/3 or worse	21 (19)	27 (21)	22.4	(−42.5, 58.3)	21 (19)	27 (21)	22.4	(−42.5, 58.3)
EGL	11 (9)	12 (9)	8.5	(−126.6, 63.4)	3 (2)	0 (0)	NA	NA
Condyloma	7 (6)	12 (9)	41.8	(−60.3, 80.6)	0 (0)	0 (0)	NA	NA
VIN 2/3 or VaIN 2/3	2 (1)	0 (0)	NA	NA	2 (1)	0 (0)	NA	NA

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; EGL = external genital lesion; NA = not applicable; qHPV = quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine; VaIN; = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia. *n* = number of cases at the end of study (mean follow-up time per subject of 3.8 years); *m* = number of cases in original report (mean follow-up time per subject of 2.2 years). Subjects are counted once in each applicable end point category. A subject may appear in more than one category.

recently RCT on vaccine efficacy in males

Recently, an RCT on the efficacy of the quadrivalent vaccine in males has been published [49]. Among other information, the study presents results on persistent infection and on DNA detection for HPV types 6, 11, 16 and 18 (see table 10.4-7).

Table 9.4-7: Efficacy against persistent infection with HPV types 6, 11, 16, or 18 and against detection of HPV DNA in the intention-to-treat-population [49]*

Variable	Quadrivalent HPV Vaccine (N = 1817)				Placebo (N = 1815)				Observed Efficacy
	No. of Subjects	Cases	Person-Yr at Risk	Rate	No. of Subjects	Cases	Person-Yr at Risk	Rate	% (95% CI)
		no.		*no./100 person-yr at risk*		*no.*		*no./100 person-yr at risk*	
Persistent infection†									
HPV type									
Type 6, 11, 16, or 18	1817	148	4094.3	3.61	1815	273	3942.6	6.92	47.8 (36.0 to 57.6)
Type 6	1817	63	4213.8	1.50	1815	112	4139.4	2.71	44.7 (24.1 to 60.1)
Type 11	1817	16	4284.6	0.37	1815	39	4238.7	0.92	59.4 (25.7 to 78.8)
Type 16	1817	71	4199.5	1.69	1815	131	4112.7	3.19	46.9 (28.6 to 60.8)
Type 18	1817	25	4267.0	0.59	1815	56	4210.1	1.33	56.0 (28.2 to 73.7)
Sexual orientation									
Heterosexual males	1542	96	3723.7	2.58	1541	187	3596.8	5.20	50.4 (36.2 to 61.6)
Males who had sex with male partners	275	52	370.6	14.03	274	86	345.8	24.87	43.6 (19.5 to 60.8)
DNA detection									
HPV type									
Type 6, 11, 16, or 18	1817	384	3851.1	9.97	1815	511	3736.5	13.68	27.1 (16.6 to 36.3)
Type 6	1817	158	4123.4	3.83	1815	239	4047.5	5.90	35.1 (20.3 to 47.3)
Type 11	1817	50	4254.0	1.18	1815	87	4202.6	2.07	43.2 (18.7 to 60.7)
Type 16	1817	189	4070.9	4.64	1815	259	4014.2	6.45	28.0 (12.9 to 40.7)
Type 18	1817	89	4205.4	2.12	1815	133	4151.5	3.20	33.9 (13.0 to 50.1)
Sexual orientation									
Heterosexual males	1542	268	3516.2	7.62	1541	379	3416.8	11.09	31.3 (19.4 to 41.5)
Males who had sex with male partners	275	116	334.9	34.64	274	132	319.7	41.29	16.1 (−8.5 to 35.2)

* Data are shown for subjects who had at least one follow-up visit after day 1. HPV denotes human papillomavirus.
† Persistent infection was defined as detection of the same HPV type (6, 11, 16, or 18) in anogenital swab or biopsy specimens collected on two or more consecutive visits, with an interval of at least 6 months (±1 month) between the visits. Subjects in whom DNA for HPV type 6, 11, 16, or 18 was detected at one or more visits were counted as cases for the DNA detection end point.

Specific subgroup analyses from quadrivalent vaccine trial data have been conducted on the efficacy against cervical disease in subjects with prior HPV infection [50] and on the impact of the vaccine on all HPV-associated genital disease in women [51]. In the former case, the information in the study may be relevant for model information that is related to natural protection after HPV infection. The latter provides information on the impact of the vaccination on diseases irrespective of the HPV-type (see table 10.4-8 for the type of information provided). However, both studies retrospectively analysed data from trials that have not originally been designed to analyse the issues in question.

Subgroup analysis also available: subjects with prior infection, impact on all HPV-associated genital diseases

Table 9.4-8: Reductions in any cervical intraepithelial neoplasia (CIN) and any external genital lesion irrespective of causal human papillomavirus (HVP) type [51]*

	Vaccine group			Placebo group			
Endpoint and population	No. of women	No. of women with a lesion	Rate†	No. of women	No. of women with a lesion	Rate†	% Reduction (95% CI)
Negative to 14 HPV types population‡							
Any CIN1 or worse irrespective of causal HPV type	4616	272	1.7	4680	390	2.4	29.7 (17.7 to 40.0)
Any CIN2 or worse irrespective of causal HPV type	4616	77	0.5	4680	136	0.8	42.7 (23.7 to 57.3)
By lesion severity							
CIN1	4616	241	1.5	4680	346	2.1	29.7 (16.9 to 40.6)
CIN2	4616	57	0.3	4680	101	0.6	42.9 (20.2 to 59.5)
CIN3	4616	36	0.2	4680	64	0.4	43 (13.0 to 63.2)
AIS	4616	0	0	4680	3	<0.1	100 (<0 to 100)
Any genital wart irrespective of causal HPV type	4689	29	0.2	4735	169	1.0	82.8 (74.3 to 88.8)
Any VIN1 or VaIN1 irrespective of causal HPV type	4689	25	0.2	4735	56	0.3	54.8 (26.4 to 73.0)
Any VIN2–3 or VaIN2–3 irrespective of causal HPV type	4689	7	<0.1	4735	31	0.2	77.1 (47.1 to 91.5)
ITT population§							
Any CIN1 or worse irrespective of causal HPV type	8562	975	3.4	8598	1199	4.2	19.1 (11.9 to 25.7)
Any CIN2 or worse irrespective of causal HPV type	8562	421	1.4	8598	520	1.8	19.0 (7.7 to 28.9)
By lesion severity							
CIN1	8562	778	2.7	8598	984	3.4	20.3 (12.4 to 27.5)
CIN2	8562	296	1.0	8598	367	1.2	19.3 (5.7 to 31.0)
CIN3	8562	237	0.8	8598	284	1.0	16.4 (0.4 to 30.0)
AIS	8562	6	<0.1	8598	16	0.1	62.5 (<0 to 88.0)
Any genital wart irrespective of causal HPV type	8689	134	0.4	8702	351	1.2	62.0 (53.5 to 69.1)
Any VIN1 or VaIN1 irrespective of causal HPV type	8689	89	0.3	8702	127	0.4	29.7 (7.2 to 47.0)
Any VIN2–3 or VaIN2–3 irrespective of causal HPV type	8689	30	0.1	8702	61	0.2	50.7 (22.5 to 69.3)

* A subject is counted only once within each applicable row. There were no cases of cervical cancer. There was one case of vulvar cancer in the negative to 14 HPV types population (vaccine arm) diagnosed 18 months post-dose 3 that is not included in this table. The lesion was negative to all tested HPV types, as described previously (7,10). AIS = adenocarcinoma in situ; CI = confidence interval; ITT = intention to treat; VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.

† Women with an endpoint per 100 person-years at risk.

‡ This population was restricted to subjects who received at least one injection of HPV6/11/16/18 vaccine or placebo and had follow-up, and, at enrollment, were seronegative and DNA negative to HPV6, 11, 16, and 18; were DNA negative to all 10 nonvaccine HPV types, including HPV31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; and had a normal Papanicolaou test result.

§ Intention-to-treat population was all subjects who received at least one injection of HPV6/11/16/18 vaccine or placebo and had follow-up, regardless of the presence of HPV infection or HPV-related disease at enrollment.

In the meantime, the results from the single trials have been summarised in systematic reviews or meta-analyses. These include a meta-analysis of the efficacy and safety of prophylactic vaccines (bivalent and quadrivalent) against cervical HPV infection and diseases among women [52], a systematic review on long-term protection against cervical infection [53] and a review of the bivalent vaccine-impact on premalignet cervical lesions [54].

systematic reviews and meta-analysis also available

The meta-analysis [52] provides pooled data for the vaccine efficacy on persistent infection and on precancerous lesions by HPV type (16, or 18) and by type of precancerous lesion (CIN1+, CIN2+). Furthermore, pooled data on cross-protection against HPV 31/33/45/52/58 in terms of infection and precancerous lesions are presented. The systematic review [53] may be relevant for additional information on the comparative antibody levels in various age-groups of the bivalent and quadrivalent vaccine. The review of bivalent vaccine studies [54] summarises evidence from phase II and phase III studies. Its additional value may be that long-term data of up to 8.4 years concerning the efficacy of the bivalent vaccine on persistent HPV infection are presented.

Safety

variety of study types on safety

Data on the vaccines' safety are provided in various different types of studies: They can be obtained from the single RCTs cited earlier, from pooled analyses of RCTs (e.g. analysis on the risk of miscarriage by Wacholder et al. [55]), from the meta-analysis on RCTs [52], from reports by public health institutes (e.g. Centre for disease control and prevention [56], Paul-Ehrlich Institut [57]) or from separate adverse event reporting studies (e.g. Van Kooster et al. [58] for the Netherlands) and from analyses of adverse events reporting systems (e.g. Slade et al. [59]). Due to the different study designs the data provided differ in their characteristics (see table 10.4-9 for an example ondata from an analysis of an adverse events reporting system).

Table 9.4-9: Most common and other selected quadrivalent HPV adverse events following immunisation in the United States, reported to VAERS June 1, 2006, through December 31, 2008 [59]

AEFI[a]	No. (%)			Total, No.	Reporting Rate[c]
	Serious Adverse Events	Nonserious Events	qHPV Alone[b]		
Syncope, syncope vasovagal	93 (5)	1803 (95)	1396 (74)	1896	8.2
Local reaction[d]	41 (2)	1700 (98)	1338 (77)	1741	7.5
Dizziness	96 (6)	1476 (94)	1147 (73)	1572	6.8
Nausea	119 (10)	1045 (90)	908 (78)	1164	5.0
Headache	150 (16)	787 (84)	688 (73)	937	4.1
Hypersensitivity reaction[e]	47 (6)	678 (94)	582 (80)	725	3.1
Urticaria	22 (4)	590 (96)	501 (82)	612	2.6
Venous thromboembolic event	39 (69)	17 (31)	55 (98)	56	0.2
Autoimmune disorder	19 (37)	32 (63)	45 (88)	51	0.2
Guillain-Barré syndrome	31 (74)	11 (26)	25 (60)	42	0.2
Anaphylaxis	8 (29)	20 (71)	18 (64)	28	0.1
Death	32 (100)	0	23 (72)	32	0.1
Transverse myelitis	10 (100)	0	10 (100)	10	0.04
Pancreatitis	9 (100)	0	9 (100)	9	0.04
Motor neuron disease	2 (100)	0	2 (100)	2	0.009

Abbreviations: AEFI, adverse event following immunization; qHPV, quadrivalent human papillomavirus recombinant vaccine; VAERS, Vaccine Adverse Event Reporting System.
[a] Using MedDRA terms. More than 1 code may be assigned to a single report.
[b] No other vaccine was coadministered.
[c] Reports per 100000 doses distributed.
[d] Local injection site reaction MedDRA codes include injection site abscess, injection site abscess sterile, injection site atrophy, injection site cyst, injection site desquamation, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site necrosis, injection site nodule, injection site edema, and injection site pain.
[e] Hypersensitivity reaction MedDRA codes include anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, cross-sensitivity reaction, dermographism, hypersensitivity, urticaria, urticaria thermal, and urticaria vesicular.

Duration of protection

longest study 8 years

The longest follow-up data are available for a monovalent vaccine (against HPV-16) that has been developed prior to the licensed bivalent and quadrivalent vaccines. The study observed immunogenicity for 8 years [60]. De Carvalho et al. [47] report efficacy and immunogenicity of the bivalent vaccine up to 7.3 years. In their tables the authors present the total number of women in the intervention and placebo group and the number of women reporting ≥1 event. Immunogenicity is described in figures only without detailed numerical data.

HPV-vaccination schedule and coverage

information on vaccination schedule from WHO and Austrian sources

The WHO report on HPV provides information on the licensure status of the bivalent and quadrivalent HPV-vaccine.

Information on the country recommendations concerning primary target groups, catch-up groups and the vaccination of males as well as on the delivery strategy can be obtained from the document published by the advisory board for the ministry of health (Oberster Sanitatsrat) [61].

WHO document provides coverage rates for other vaccines

Since the HPV-vaccination has not been publicly funded so far, figures on the current proportion of coverage are not available for Austria. Consequently, figures on the proportion of coverage for a publicly funded HPV-vaccination programme need always be based on assumptions. Published data source to obtain estimates for these assumptions are published proportions in other publicly funded vaccination programmes. Such figures have been published in the WHO report on HPV [28] Figure 10.4-2 and figure 10.4-3 demonstrate examples for diphteria, tetanus and pertussis and for measles.

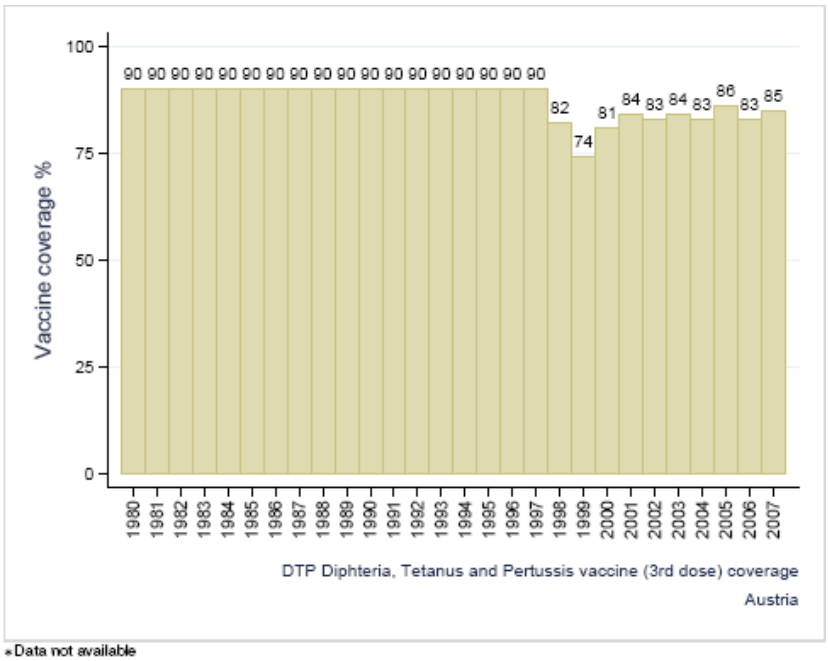


Figure 9.4-2: Diphteria, Tetanus and Pertussis coverage (3rd dose completed) in Austria [28]

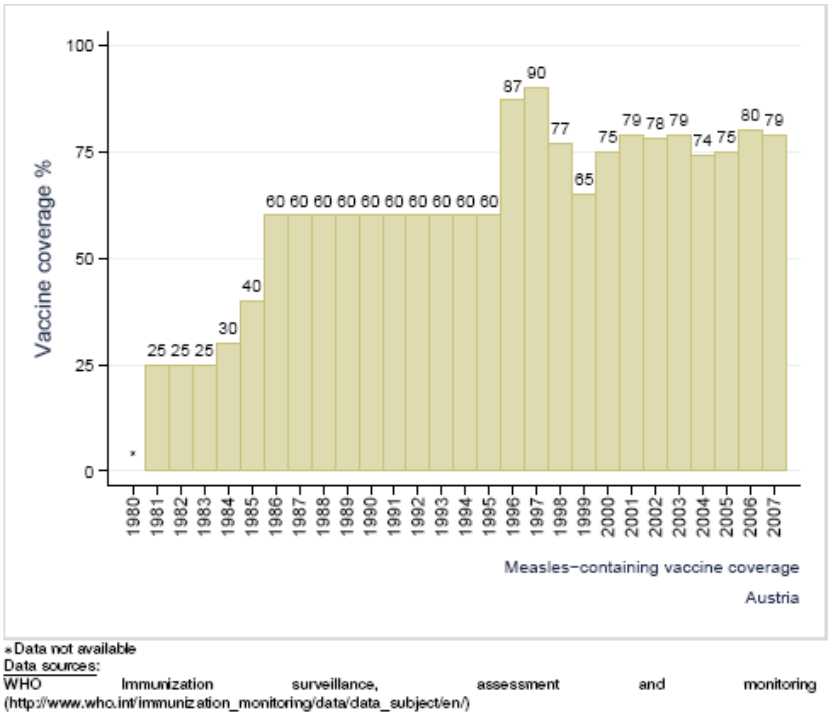


Figure 9.4-3: Measles-containing vaccine coverage in Austria [28]

9.5 Data on sexual activity

no Austrian data available on sexual activity

The WHO report from 2010 states that no Austrian data are available on sexual behaviour (e.g. onset of sexual intercourse, high-risk sexual behaviour). Some data are provided on reproductive health behaviour in Austria (e.g. on the use of contraception, age of marriage) that are themselves extracted from published secondary sources such as reports from the World Bank or the United Nations [28].

9.6 Data on resource utilisation

6 resource categories

According to the ‚2007 report on HPV vaccination modelling' [16] the following resource categories need to be taken into account for calculating the direct costs

- Routine screening using pap smear
- Diagnostic follow-up in women with positive pap smears
- Management/treatment of precancerous lesions (especially CIN 3)

- Diagnostic procedures for invasive cervical carcinomas
- Treatment of invasive cervical carcinomas
- Vaccination

data source: routine data, clinical practice guidelines and expert opinions

As summarised in chapter 7, appropriate data sources for resource use patterns are routine data, clinical practice guidelines and expert opinions. For the purpose of this report, clinical practice guidelines are the only published secondary data source that is relevant.

2 relevant guidelines

Currently, there exists one published guideline on the diagnostic and treatment of precancerous lesions [62] and one on the treatment of invasive cervical carcinoma [63].

information on resource categories can be obtained

From both guidelines, information on the types of diagnostic procedures used and on the treatment methods applied can be obtained. Hence, they are helpful for identifying relevant resource categories and technologies that need to be taken into account in the model and for which information on unit costs need to be collected.

no quantitative information or info on discrepancies to real life practice

The guidelines do not provide information on the number of women that are diagnosed with precancerous lesions or on the number of women with invasive carcinoma nor do they provide information on which proportion of women receives which type of treatment in the case of alternative options. Finally, no information can be obtained from the two guidelines on the potential discrepancies between the recommendations in the guidelines and the real world practice patterns.

9.7 Data on unit costs

data on unit costs not from published literature but from…

According to the information from the chapter 7, data on unit costs need to be country-specific and, thus, they will hardly be found in published literature.

…routine data

In the case of HPV-vaccination no appropriate published document that provides information on relevant unit costs for HPV-vaccination modelling has existed prior to the HTA-report from 2007. Hence, the primary data sources for Austrian-specific unit costs will be databases on tariffs (Honorarordnungsdatenbank) and routine data (e. g. to obtain information on hospital charges). As it has been stated in the method section, these data sources will not be described in this report.

earlier report provides summary on unit costs

In the case of HPV-vaccination modelling, both, a report [16] and a paper [64] have been published that provide detailed information on unit costs in the appendix of the report and in table 2 of the paper.

10 Discussion

In chapter 10, the guidance on possible relevant data sources that has been summarised in the first part of this report has been applied to the case of 'HPV vaccination modelling'.

guidelines are helpful as starting point but…

Generally, the guidance was of help in identifying the starting point for the data search and in getting an idea on what type of data sources may be used for what type of model parameters. In particular, the summary showed for what model parameters secondary published literature may be the preferred first choice (e.g. for parameters dealing with efficacy) and for which types of parameters other secondary data will likely be appropriate (e.g. for parameters on costs).

…researchers with little experienced will need more info

Yet, because none of the manuals provided detailed information on the strengths and weaknesses of those data, the guidance may not be of enough support for persons that are little acquainted with the subjects involved such as clinical epidemiology.

case study showed limitations of guidance

Moreover, some limitations appeared when it came to the specific application in a modelling exercise. For example for data on the natural history of the disease, manuals recommend observational studies/disease registries. Due to the nature of the disease and the available treatment options such studies are hardly available in the case of cervical cancer and the few studies that exist are more than 20 years old and may not be transferable to the current female population. Hence, the recommendations in the manuals will not be applicable to every single case.

how to deal with conflicting data from more than one source?

Furthermore, some data that are presented in the published documents are conflicting. For example the data on cervical carcinoma incidence and mortality from the WHO document [28] in chapter 10.3.2 are different from those presented by the 'Statistik Austria' [65] where mortality and incidence rates are lower than in the WHO document. The manuals provide only limited information on how to deal with conflicting data although the issue was briefly mentioned in context with expert opinions that may be useful in such situations.

data may not be detailed enough

Although a number of data have been identified in published papers and reports, these data my not be detailed enough for parameterising the 'HPV vaccination' model. For example, one document on cervical cancer [20] states that the time period between infection and precancerous lesions is approximately 10 years without further details on risk differences that may depend on the HPV genotype. One may therefore at least need to check the references cited in this document for further information or more detailed data. Another example are the data from clinical studies. They are usually presented in an aggregated way while information would often be needed on specific subgroups or patient characteristics (e.g. smoking status, age).

thorough check of data context required before using them

Additionally, before using data that have been presented in chapter 10 in the modelling exercise, the context where they have been extracted from needs to be taken into account carefully. For example, modellers need to check thoroughly on what type of analysis vaccine-efficacy data are based on (e.g. per protocol analysis, intention-to-treat analysis).

some data are missing at all

For a number of issues (such as the process of HPV transmission), data are generally missing. For other data categories, specific *Austrian* data are miss-

ing (such as prevalence or incidence of precancerous lesions) and, finally, in many cases data may not be in the format that is needed for the model.

published literature only one piece of information, further processing requires experts

Hence, published literature can only provide one piece of a jigsaw in addition to further sources of information. Additionally, the methods from chapter 8 on how to further process the data may be useful, however they need to be applied in cooperation with the relevant experts to guarantee high modelling standards.

limitations of report: literature not based on systematic search, no quality check of data

Finally, the limitations of this report need to be taken into account when using the information for the ongoing modelling exercise. Firstly, the literature cited is not based on a systematic literature search for every single information category. Secondly, the studies have not been subject to a quality check.

11 Conclusion

report summarises guidelines on how to identify data for models

This report summarises the current modelling guidelines that are used within the context of HTA in terms of how to identify data for parameterising models, in terms of possible relevant types of data and in terms of further data processing methods.

intended as a starting point

While the report is not to be regarded as exhaustive, it is intended to provide a starting point for developers of models to ensure a structured and methodological sound approach to building decision-analytical models for HTA.

handling of data requires interdisciplinary process…

Since the correct handling of the different types of data requires many different experts from various disciplines, this report cannot replace a continuous process of knowledge exchange between experts from HTA, epidemiologists and modelling specialists in Austria during a modelling project.

e.g. between HTA information specialist and modeller

One part of such a dialogue may be the cooperation between the information specialist in an HTA unit and the model developer. Another part of cooperation may be between the model-developer and statisticians that are familiar with clinical epidemiology.

Iterative process needed for using data in HPV-model

Hence, the data that are provided for the HPV-vaccination model exercise in chapter 10 need now to be handled further by the model developers in an iterative process with the other partners involved.

12 Literature

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