Standard Operating Procedure

of the

German Standing Committee on Vaccinations (STIKO)

for the systematic development of vaccination recommendations

Version 2.0

February 6, 2014

Content

1. Introduction and summary

This standard operating procedure (SOP) describes the methodological concepts and steps used by the German Standing Committee on Vaccinations (STIKO) and serves as guidance for STIKO in the development of new vaccination recommendations. If there is a need for minor modifications to existing vaccination recommendations, the designated working group—in consultation with STIKO—decides which steps from this SOP are to be applied and to what extent. The present document reflects the current status of the methodological discussions within STIKO and the STIKO methods working group, and it will be updated if necessary.

The mainstay in the development of a vaccination recommendation by STIKO is a risk-benefit assessment. Besides individual risks and benefits, STIKO considers risks and benefits on the population level, for example herd protection effects, the possibility of eliminating a disease if high vaccination coverage is achieved, potential pathogen replacement phenomena, or likely shifts in the age distribution of cases acquiring the targeted disease if a vaccination program is implemented. In addition, STIKO may integrate the results of economic evaluations in its decision-making process if the studies are applicable to the German healthcare setting.

When assessing vaccines and developing vaccination recommendations, STIKO usually conducts systematic literature reviews and applies the concept of evidence-based medicine (EBM). For the development of recommendations, STIKO also uses the approach of the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) Working Group. Traditionally, EBM has been applied in clinical settings where an intervention in patients with specific symptoms/disease is assessed in comparison with a therapeutic alternative. For the development of a vaccination recommendation, STIKO usually compares scenarios of "vaccination" vs. "no vaccination," but takes alternative preventive measures into consideration, if available.

According to EBM criteria, a systematic review consists of five steps that are likewise used by STIKO for the development of vaccination recommendations:

i) Formulation of specific questions und operationalization of their components;
ii) Systematic literature review and identification/selection of relevant studies;
iii) Quality assessment of the available evidence derived from the identified literature based on defined criteria;
iv) Translation of the knowledge gained into the pertinent setting (from evidence to recommendation);
v) Evaluation of the implemented measure and modification of the recommendation if needed.

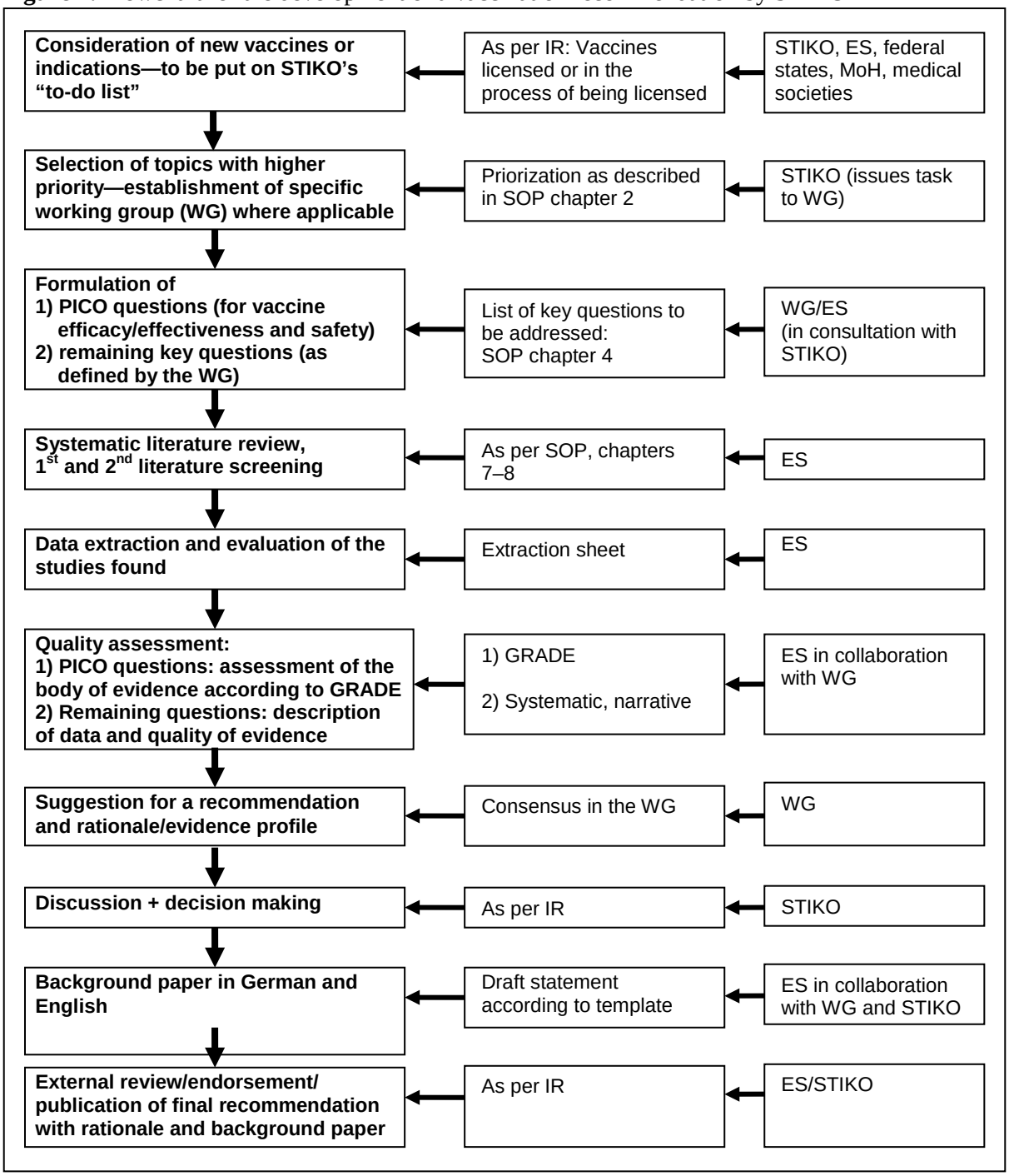
Following EBM, the assessment of an intervention begins with the formulation of a specific patient-relevant (or population-relevant) question or problem. The question (in the so-called "PICO" format) should usually include four aspects: the population (P) or individual, the intervention (I), the comparison (C), and a specific outcome (O). Both individual-relevant and population-relevant outcomes will be assessed in the context of the development of a vaccination recommendation.

EBM specifically refers to the best evidence currently available. The gold standard for the assessment of the available evidence related to a clinical intervention is a systematic review of randomized controlled trials (RCTs). However, for many important questions in the immunization field, only data from observational studies are available. Whenever reasonable, evidence generated from observational studies can be incorporated into the GRADE

methodology. The GRADE methodology is especially suitable for questions related to vaccine efficacy and safety.

The following figure depicts the steps applied by STIKO to develop a vaccination recommendation, including both methodologies and responsibilities (from right to left in the figure, the boxes indicate who is responsible/initiating, how the step is performed, and the result of this action).

Figure 1: Flowchart for the development of a vaccination recommendation by STIKO



ES: executive secretariat of STIKO; MoH: Ministry of Health;WG: STIKO working group; IR: internal regulations endorsed by STIKO

2. Topic selection and prioritization

The vaccine market is highly dynamic, with many new vaccines having received market authorization in recent years or currently being in the advanced development pipeline. Therefore, and because of the limited personnel and financial resources of STIKO, it is necessary to prioritize topics and decide on the order in which they need to be addressed by a topic-specific working group (WG) and the executive secretariat (ES). Thus, the following criteria need to be fulfilled for a topic to be included on the STIKO task list and considered for prioritization:

Criteria for consideration in the prioritization process:

a) Availability of a vaccine
- In principle, any vaccine licensed for the German market qualifies for discussion by STIKO.
- For vaccines with a high degree of public interest, STIKO can form a working group and start the assessment process prior to licensure.

b) The disease burden in Germany is quantifiable
- Disease incidence (if possible/indicated, stratified by age group or disease severity)
- Number of deaths or mortality, number of hospitalizations, risk of long-term sequelae

c) Availability of data on vaccine efficacy/effectiveness and safety
- Published studies on vaccine efficacy/effectiveness, preferably peer-reviewed, should be available prior to assessment.
- Published data on reactogenicity and adverse events following vaccination, preferably peer-reviewed, should be available prior to assessment.

All topics that need a systematic assessment by a STIKO WG or the ES have to be included in the prioritization process. This includes the development of new vaccination recommendations as well as updating existing recommendations. As part of the prioritization process, STIKO weighs the topics on the task list and decides on the order for topic assessment. Besides expected work load, the following aspects might be considered:

a) Rough estimate of the burden of disease

b) Public interest in the vaccination recommendation (see Appendix D)

c) Benefits/risks of a respective vaccination program

- Potential effects of the vaccination (effectiveness and safety) as well as total effects at population level
- Perception of the health problem by health professionals and the general public
- Expected acceptance of the vaccination in the target population

d) Integration of the new vaccine in the national immunization schedule: Will data be available in the near future that will have a significant effect on the decision? Are other scientific committees (e.g., other national immunization technical advisory groups, the WHO, etc.) in the process of assessing the available evidence?

e) Should further important analyses be commissioned (e.g., modeling)?

3. Involved groups and tasks

3.1 STIKO

The Committee generally holds non-public meetings twice per year. According to defined criteria (see chapter 2), STIKO prioritizes topics to be addressed. At the start of the three-year appointment period, this prioritization is undertaken. If necessary, the prioritization list can be

updated. The data needed for the prioritization process are summarized by the responsible topic-specific STIKO WG in cooperation with the ES. If no WG exists, the ES summarizes the data. Depending on the results of the prioritization process, STIKO commissions topic-specific WGs, where applicable, to review and grade the quality of available evidence and to develop a background paper and a proposal for a vaccination recommendation. The WG presents progress reports to STIKO on a regular basis until the final discussion and informed decision making by STIKO on the specific topic is possible.

3.2 STIKO working groups

STIKO establishes working groups (WGs) for a specific vaccination, indication, or problem.

The WG usually consists of the following:

- 2–4 STIKO members (including a speaker)
- 1–2 staff members of the ES
- external experts who are appointed by the WG as needed (e.g., representatives of the relevant National Reference Laboratory or clinicians/scientists with a specific expertise in the relevant field of work)

STIKO members with a potential conflict of interest regarding a specific vaccination indication cannot become members of that WG. Like external WG experts, they can participate in WG meetings to inform the WG, but they do not take part in the final WG decision-making process regarding the draft recommendation.

When asked to develop a new or modified vaccination recommendation, the first step taken by the WG is generally to define the vaccination goal (see chapter 5). Based on STIKO's set of key questions (chapter 4), the WG obtains an overview of aspects to be incorporated in the assessment of the available evidence regarding the disease to be prevented and the vaccination. Depending on the task to be performed (new recommendation or updating an existing recommendation), the WG decides for which of the key questions an exploratory or systematic literature review will be conducted. For questions on vaccine efficacy/effectiveness and safety, systematic reviews should be conducted after the formulation of PICO questions by the WG (see chapter 6), and the quality of the evidence should be assessed by applying the GRADE methodology.

Based on the available data and information from the identified literature, the WG addresses all questions relevant to the development of the new or modified vaccination recommendation, assesses the quality of the available evidence, and prepares a draft recommendation to be proposed to STIKO. STIKO then debates the draft by considering all relevant key questions and criteria.

3.3 The executive secretariat

Based on the WG's PICO questions addressing vaccine efficacy/effectiveness and safety and other relevant key questions, the STIKO executive secretariat (based in the immunization unit of the Robert Koch Institute) develops a literature search strategy in close collaboration with the WG and subsequently conducts systematic or exploratory literature reviews considering the previously agreed inclusion and exclusion criteria. Relevant information from each study included in the analysis is systematically summarized using a data extraction form (chapter 9). Furthermore, study quality is evaluated according to standardized criteria. Processes and decisions relevant to the development of the vaccination recommendation (e.g., structure of the literature review and its results) should be documented throughout.

Finally, the ES prepares a systematic review that summarizes the findings and develops evidence profiles (chapters 8–10). These are incorporated in a background paper that is to serve as a basis for the development of the recommendation for or against the vaccination under discussion. If the recommendation proposed by the WG is adopted by STIKO, the ES drafts the final recommendation with its scientific rationale and the background paper in collaboration with the WG (chapter 12).

4. Key questions to be addressed

A set of key questions was developed by STIKO as a guideline for the development of a vaccination recommendation. These questions are as follows:

I. Questions related to the pathogen

- What are the characteristics of the pathogen causing the target disease?
- What pathogen subtypes/serotypes exist, and what is their local epidemiology?

Procedure: *Exploratory literature review including standard literature. Systematic or exploratory review of epidemiological data for Germany or Europe according to the specifications of the WG. Utilization of surveillance data (derived from the national mandatory disease reporting system in Germany) and other data sources (e.g., sentinel systems, reference laboratories, international cooperation partners).*

II. Questions related to the target disease

- What is the burden of disease (incidence, hospitalization, mortality, seroprevalence, complications, and disabilities, if applicable stratified by risk groups/serotypes)?
- What is the perception of the target disease in the population?

Procedure: *Utilization of surveillance data (derived from the national mandatory disease reporting system in Germany) and other high quality data sources for Germany. Where appropriate, supplemented by data from other European countries, identified by exploratory or systematic reviews of German or European data sources according to the specifications of the WG. Consideration of surveys on the perceptions of the target disease in the population, if available, or initiation of surveys when indicated.*

III. Questions related to the vaccine(s)

- What is the scope of licensure (age groups, vaccination schedule, and target diseases)?
- What is the efficacy/effectiveness in preventing defined outcomes in clinical trials or observational studies, when indicated stratified by age and risk group?
- What is the vaccine safety profile?
- Questions on duration of protection; necessity of booster vaccinations; co-administration with other vaccines; if only studies on immunogenicity are available, quality of the (serological) correlate of protection.

Procedure: *Systematic literature review for PICO questions on the efficacy/effectiveness and safety of the vaccine as defined by the WG. Application of GRADE to the assessment of the quality of evidence. Only where indicated, inclusion of effectiveness and safety data from unpublished studies, after release from confidentiality by the Paul-Ehrlich-Institute (German Federal Regulatory Authority) or when provided by the pharmaceutical company.*

IV. Questions related to the immunization strategy

- What is/are the immunization goal(s) that should be achieved?
- What are possible barriers to the success of the vaccination recommendation?

- What is the number needed to vaccinate (NNV) in regard to different outcomes?
- What are potential positive or negative effects of a vaccination program on the population level (e.g., herd immunity, age shift, replacement)?
- What is the vaccination coverage needed to induce positive population-level effects?
- What experiences with comparable vaccination recommendations are available from other countries (transferable to Germany?)?

Procedure: *Review of published literature, when indicated or possible, own calculations or mathematical modeling preferable. Consideration of data/models from other national or international research groups.*

V. Questions related to the implementation of a vaccination recommendation

- Can a potential vaccination recommendation be implemented?
- Acceptance of the vaccination and recommendation in the population/among medical professionals
- Estimation of costs: if valid data are available, STIKO can compare the costs of the intervention with the costs of the disease. If possible, results from a suitable cost-effectiveness analysis can be considered.
- What are alternative preventive measures to reach the vaccination goal? In comparison with vaccination, how effective and implementable are the alternative measures?
- Do systems exist to monitor the degree of the implementation of the recommendation and evaluate the effects of vaccination?

Procedure: *Utilization of manufacturer-independent studies (models) that are specific for the German healthcare system. Exploratory literature review regarding effectiveness and safety of alternative preventive measures. Expert opinion.*

VI. Final assessment

- Is there a public interest in the vaccination recommendation (see Appendix D)?
- Overall epidemiological risk-benefit assessment

Procedure: *Consensus in STIKO by weighing the results from question set I–V*

5. Formulation of the vaccination goal

As the first step in the process of developing a vaccination recommendation, STIKO, or the WG in consultation with STIKO, formulates a specific vaccination goal to be achieved in Germany with the new recommendation. For the formulation of the vaccination goal, outcomes should be considered that were judged as essential during the development of PICO questions (e.g., reduction of hospitalizations due to a certain pathogen; see chapter 6). When defining the goal, consideration should also be given to data required to monitor the success of the implementation in the future.

6. Development of PICO questions

The commissioned WG identifies patient- and population-relevant outcomes specifically for the questions related to vaccine effectiveness and safety, which are perceived as pivotal for the development of the recommendation. According to the GRADE methodology, the members of the WG rate these outcomes on a scale from 1 to 9 as “critical” (7–9 points), “important” (4–6 points), or of “limited importance” (1–3 points) for decision making. The WG formulates the appropriate PICO questions according to the vaccination goal and corresponding target population (PICO = “patient, intervention, comparator, outcome”; see

introduction). Before starting the literature review, all STIKO members have the opportunity to comment on the PICO questions developed by the WG. For every PICO question, the WG identifies the study designs suitable for addressing the specific questions. The systematic literature search can be limited to publications with these specific study designs.

7. Systematic literature review

The systematic literature review including extraction of the relevant data is the centerpiece of the systematic development of a vaccination recommendation. Systematic and/or exploratory literature reviews are conducted according to the set of key questions (chapter 4) and the specific PICO questions formulated by the WG. The ES staff decides on the search strategies in close collaboration with the WG and performs the literature searches. For quality control, the review and evaluation of identified studies can be conducted in cooperation with or after consultation of external experts (e.g., the German Cochrane Center). If available, published systematic reviews of high quality can be used. If necessary, such reviews will be updated and their methodological quality will be assessed, using established instruments (e.g., the AMSTAR checklist). Using central registers (such as PROSPERO), it will be checked whether other groups have started to perform a relevant systematic review. The protocol of a new systematic review can be stored in such a register. The WG can also contract out the systematic literature review to external institutes if these guarantee high standards of scientific quality.

The following databases and approaches are used for a systematic literature review (a compilation of some of these databases can be found in chapter 6 of the Cochrane handbook):

- MEDLINE, EMBASE, and other relevant databases depending on the study question.
- Cochrane Collaboration Database for RCTs (The Cochrane Central Register of Controlled Trials, CENTRAL). The database also includes studies that have been published only in conference reports or other, non-electronic sources.
- Systematic review database of the Cochrane Collaboration. The database already contains a number of vaccine-related reviews that can be updated by the ES if needed.
- HTA databases (containing Health Technology Assessment reports) of the Cochrane Collaboration and the National Institute for Health Research.
- Manual search of further studies cited in the reference section of included publications.

8. Identification of relevant studies

The relevant WG (in collaboration with the STIKO methods WG if appropriate) initially decides on the study selection criteria (e.g., study design, study periods, geographic area). According to international guidelines, the selection of relevant studies is conducted by two independent reviewers (usually from the ES or immunization unit at RKI) in two steps:

First, the reviewers screen the titles and abstracts of the studies identified in the systematic literature search. Irrelevant studies are excluded.

Second, a more intense screening process follows. The full text of the remaining studies is reviewed, and the previously determined inclusion and exclusion criteria are applied, depending on the key question to be addressed. In case of discrepancy in the assessment between the two reviewers regarding identification, inclusion, or evaluation of the literature, both members jointly come to a consensus (if necessary in cooperation with the WG).

8.1 Documentation of search strategy and results

The literature search strategies and the criteria for study inclusion and exclusion are recorded in a separate document. This should also include the number of studies identified in the different steps of the literature search, screening, and selection process. Based on this information, a flow chart should be prepared. This document should be made available as an appendix to the background paper.

9. Data extraction and evaluation of included individual studies

Using a standardized extraction sheet (see Appendix A), relevant data including those that are needed to estimate the strength of the effect of the intervention are extracted from the individual studies. The extraction sheet also contains criteria for the assessment of internal and external validity of the study, systematic review, or meta-analysis, with emphasis on the risk of systematic bias and confounding. Checklists (quality appraisal tools) developed for the respective study designs (for RCTs: "Risk of Bias Tool" of the Cochrane Collaboration; for observational studies: tools of the Critical Appraisals Skills Programme (CASP)) are used to assess risk of bias.

10. Information synthesis

In collaboration with the relevant STIKO WG, the ES prepares an information synthesis (if possible by conducting a meta-analysis) to assess the strength of the effect of the intervention on different outcomes.

10.1. Evaluation of available evidence related to PICO questions using GRADE

An evidence profile including the description of available evidence regarding the previously determined PICO questions should be generated using the software "GRADEprofiler" (an example is given in Appendix B). The software displays outcome-specific effect estimates (Summary of Findings) and the assessment of the quality of the available evidence.

The quality assessment refers to the relevant PICO question and takes into account the total body of evidence and not individual studies. When grading the quality of evidence (which is the confidence in the estimate of the effect) four levels are applied (ranging from + = "very low quality of evidence" to ++++ = "high quality of evidence"). Initially, evidence derived from RCTs receives a ++++ level in the evidence assessment. However, a downgrading can be performed based on specific criteria (Table 1). Observational studies (e.g., case control studies and cohort studies, but also "before-and-after analyses" of passive surveillance data) are initially graded as ++. An upgrading or downgrading is possible according to the same set of criteria (see Table 1 and Appendix C).

The criteria for upgrading usually apply only to evidence that is derived from observational studies. Only evidence from studies with no threats to validity (i.e., not downgraded for any reason) can be upgraded. The overall level of evidence across all outcomes is defined by the lowest level among all critical outcomes. Further details on the criteria listed in Table 1 can be found in Appendix C.

10.2. Further evaluations of relevant studies

PICO questions will usually not be formulated for key questions unrelated to vaccine safety and effectiveness (e.g., burden of disease, acceptance of a vaccine, and cost-effectiveness of a vaccination program), and these question will not be assessed according to the GRADE

methodology. To answer these questions, data from relevant studies identified in a systematic and/or exploratory literature search targeting the relevant topic are extracted (using an extraction sheet where applicable), documented, assessed, and summarized when indicated. The quality of the evidence from included studies is narratively assessed based on the study designs and relevant strengths and weaknesses. Finally, study results generated in other populations are evaluated in terms of their relevance to the target groups for vaccination in Germany (external validity). If results from several studies (e.g., concerning burden of disease) vary, a sensitivity analysis can be performed to determine the effect of the variance on a decision for or against a recommendation.

Table 1: Overview of criteria for downgrading or upgrading the quality of evidence for defined outcomes based on the body of evidence (according to GRADE).

<table>
<tr><th>Level of evidence</th><th>Study design defining the entry level</th><th>Criteria for downgrading</th><th>Criteria for upgrading</th></tr>
<tr><td>++++</td><td>RCTs</td><td rowspan="4">1) Risk of bias
-serious (-1)
-very serious (-2)

2) Inconsistency
-serious (-1)
-very serious (-2)

3) Indirectness
-serious (-1)
-very serious (-2)

4) Imprecision
-serious (-1)
-very serious (-2)

5) Publication bias
-suspected (-1)
-strongly suspected (-2)</td><td rowspan="4">1) Large effect
-large (+1)
(i.e., OR/RR > 2 or < 0.5
or vaccine effectiveness > 50%)
-very large (+2)
(i.e., OR/RR > 5 or < 0.2
or vaccine effectiveness > 80%)

2) Evidence for dose-response relationship
At population level, magnitude of disease burden or incidence relate to the level of vaccination coverage
- yes (+1)

3) plausible confounding would diminish the observed effect*
- (+1)</td></tr>
<tr><td>+++</td><td></td></tr>
<tr><td>++</td><td>Observational studies
(including case control studies, cohort studies, self-controlled case series, surveillance data)</td></tr>
<tr><td>+</td><td></td></tr>
</table>

RCT: randomized controlled trial; OR= odds ratio; RR = relative risk
*i.e., control for confounding would result in a stronger association than is actually observed

11. Synthesis of results and decision making

After the ES compiles the comprehensive background paper (using a standardized report format that aligns with the current STIKO set of key questions), the WG conducts a final assessment of the available evidence. Based on this, the WG develops a draft recommendation for or against a vaccination. This draft will be proposed, discussed, and voted on during a subsequent STIKO meeting by considering all compiled study results together with the evaluation of the quality of evidence, and by considering again the particular public interest.
STIKO does not categorize the recommendation as “weak” or “strong” (as recommended by GRADE). The following categories are applied:

- STIKO decides to include the vaccination under consideration in the vaccination recommendations.
- STIKO decides to not include the vaccination under consideration in the vaccination recommendations.

According to the standing orders of STIKO (Geschäftsordnung (§8)), a STIKO decision is made if the majority of STIKO members vote in favor of it.

After a decision has been made, the ES summarizes the evidence in a background paper in German and English. The decision, along with the rationale and background paper, are sent to stakeholders (Superior Local Health Authorities, Joint Federal Committee) for comments. These comments will be forwarded to STIKO. After a final discussion, STIKO makes an ultimate decision regarding the new recommendation.

Beyond the recommendations issued by STIKO, there may be further indications for vaccination based on existing vaccine licensures and their approved indications. These may be beneficial for an individual based on his/her particular health situation. Thus, the absence of a STIKO recommendation should not deter a physician from offering a particular vaccine if there is a well-grounded indication.

12. Publication

The current STIKO recommendations are published once a year in the national epidemiological bulletin ("Epidemiologisches Bulletin") of the Robert Koch Institute (since 2013 usually in issue 34) and on the RKI website (www.stiko.de; English versions at www.stiko.de/en). The intention is to provide a quick and systematic overview for the expert community. Usually, in the following issue of the bulletin, a summary and scientific rationale of what is new as compared with the previous publication is published.

In principle, a new STIKO recommendation will first be published in the national epidemiological bulletin. The background paper in German will also be published immediately after (or if applicable at the same time) in the epidemiological bulletin. An English version of the background paper that is identical in content is usually published in the "Bundesgesundheitsblatt" (when indicated, also in another open access journal) and should be published after the German background paper or, if possible, at the same time, and be available open access online. Members of the WG (and, if applicable, further experts who contributed significantly to the publication) should be named as authors. Both publications (the background paper in German and English) will reference each other.

If an existing vaccination recommendation was updated or underwent minor changes, it has to be decided—depending on the size of the evidence base—whether the rationale and/or background paper will be published in German only or also in English.

If STIKO decides to not include the vaccination in their recommendations, the available evidence and the assessment of the study results, as well as the scientific rationale and background paper are still prepared and published as described above.

13. References

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14. Appendices

A. Extraction sheet draft
B. Example of an evidence profile table
C: GRADE criteria for study quality upgrading and downgrading
D: STIKO definition of the term “particular public interest” as related to a vaccination (as of August 29, 2011)

Appendix A: Template for an extraction sheet

Data variables accounted for in the extraction of included studies (based on an extraction tool developed by WHO's SAGE)

Data extraction sheets are created for every systematic review. The following data fields are indicators that should be considered for each data extraction, if applicable.

Comments

1. Study, author, year

2. Name of the reviewer (only for internal use)

3. Date of extraction (only for internal use)

4. Methods

4.1. Study design

4.2. Study period

4.3. Subjects/patients/study collective/source of sample

4.4. Sample size

4.5. Inclusion/exclusion criteria

4.6. Non-respondents/lost to follow-up

4.7. Which parts of the study were prospective

4.8. Analysis procedure (per protocol, intention-to treat, subgroup analysis)

5. Study participants

5.1. Number of cases, number of controls

5.2. Definition of controls

5.3. Source of controls

5.4. Setting (cases/controls)

5.5. Country, region (cases/controls)

5.6. Age (range, mean/median) (cases/controls)

5.7. Gender (% male/female) (cases/controls)

5.8. Ethnicity (cases/controls)

5.9. Comparability of cases and controls

5.9.1. Potential confounders identified

5.9.2. Baseline assessment of outcome variables

6. Group allocation of cases and controls

6.1. Randomization

6.1.1. Sequence generation

6.1.2. Allocation sequence concealment

6.1.3. Blinding

6.2. Allocation by:

7. Intervention/treatment

7.1. Vaccine (composition, dosage, etc.)

7.2. Length of observation

8. Endpoints/outcomes/results

8.1. Definition of outcomes

8.1.1 Effectiveness

8.1.2 Safety/adverse events

8.1.3 Other outcomes

8.2. Intervals of outcome measurements, measurement of values

8.3. Validity

8.4. Reproducibility

8.5. Quality control

8.6. Missing/incomplete data

8.7. Selective reporting

9. Result summary

10. Summary of a potential risk of bias

10.1. Selection bias

10.2. Information bias

10.3. Further potential biases (e.g., Hawthorne effect)

10.4. Confounding

11. Study funding

Appendix B: Example of a GRADE evidence profile

– Using the software “GRADEprofiler”

Author(s): STIKO AG "Disease X"
Date: 2011-10-20
Question: Should Vaccination X vs no vaccination be used in children below 5 years of age?
Settings: Germany
Bibliography:

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination X	no vaccination	Relative (95% CI)	Absolute		
Death due to Disease X												
3	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	2/400 (0.5%)	8/400 (2%)	RR 0.25 (0.04 to 1.26)	15 fewer per 1000 (from 19 fewer to 5 more)	⊕⊕OO LOW	IMPORTANT
Hospitalization due to Disease X												
5	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[3]	100/7000 (1.4%)	700/8000 (8.8%)	RR 0.15 (0.12 to 0.19)	74 fewer per 1000 (from 71 fewer to 77 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Moderate inconsistancy/heterogeneity in the effect between the 3 included studies

[2] 95%CI of the pooled analysis of the Risk Ratio includes 1

[3] Large effect (pooled vaccine effectiveness in preventing hospitalization: 83%)

Appendix C: GRADE criteria for upgrading or downgrading the quality of evidence (adapted from Schünemann, ZEFQ 2009; 103: 391–400)

Criteria	Explanation
Downgrading of quality	
Limitations of study design or conduct (risk of bias)	Lack of blinding at randomization; high lost to follow-up; incomplete follow-up; no intention-to-treat analysis; lack of blinding at outcome assessment, etc.
Inconsistency (heterogeneity) of results	Large, unexplained differences in treatment effects between studies
Indirectness	Indirect comparison: Only placebo-controlled comparisons between two interventions, no head-to-head comparison. Study population, intervention, and endpoint do not exactly match the PICO question (e.g., serological parameters used as a surrogate to measure vaccine effectiveness)
Imprecision	Wide confidence intervals because of a small number of patients and/or events
Publication bias	High likelihood of missing publications with negative study results. Risk is increased in meta-analyses with small and/or industry-funded studies.
Upgrading of quality	
Large or very large effect	High-quality observational studies with direct evidence. A relative risk/odds ratio > 2 or < 0.5 corresponds to a large effect; a relative risk/odds ratio > 5 or < 0.2 indicates a very large effect.
Unlikely explanation of an effect by confounding	All remaining plausible confounders would have reduced the observed effect or would have enhanced an absent effect
Dose-response relation	Detection of a dose-response relation (e.g., significantly increased effect of a vaccination on the burden of diseases in a population with higher vaccination coverage)

Appendix D: STIKO definition of the term “particular public interest” in relation to a vaccination (as of August 29, 2011)

The term “particular public interest” is defined by STIKO as follows:

A particular public interest concerning a vaccination is present if at least one of the following criteria is met:

- The vaccination can prevent deaths, severe disease, or long-term sequelae (individual protection)
- The vaccination goal requires the development of herd protection effects
    - for individuals who cannot be vaccinated, or
    - for the elimination or eradication of a disease or a pathogen
- The vaccination is clearly able to reduce the risk or intensity of an epidemic that can significantly disrupt public life