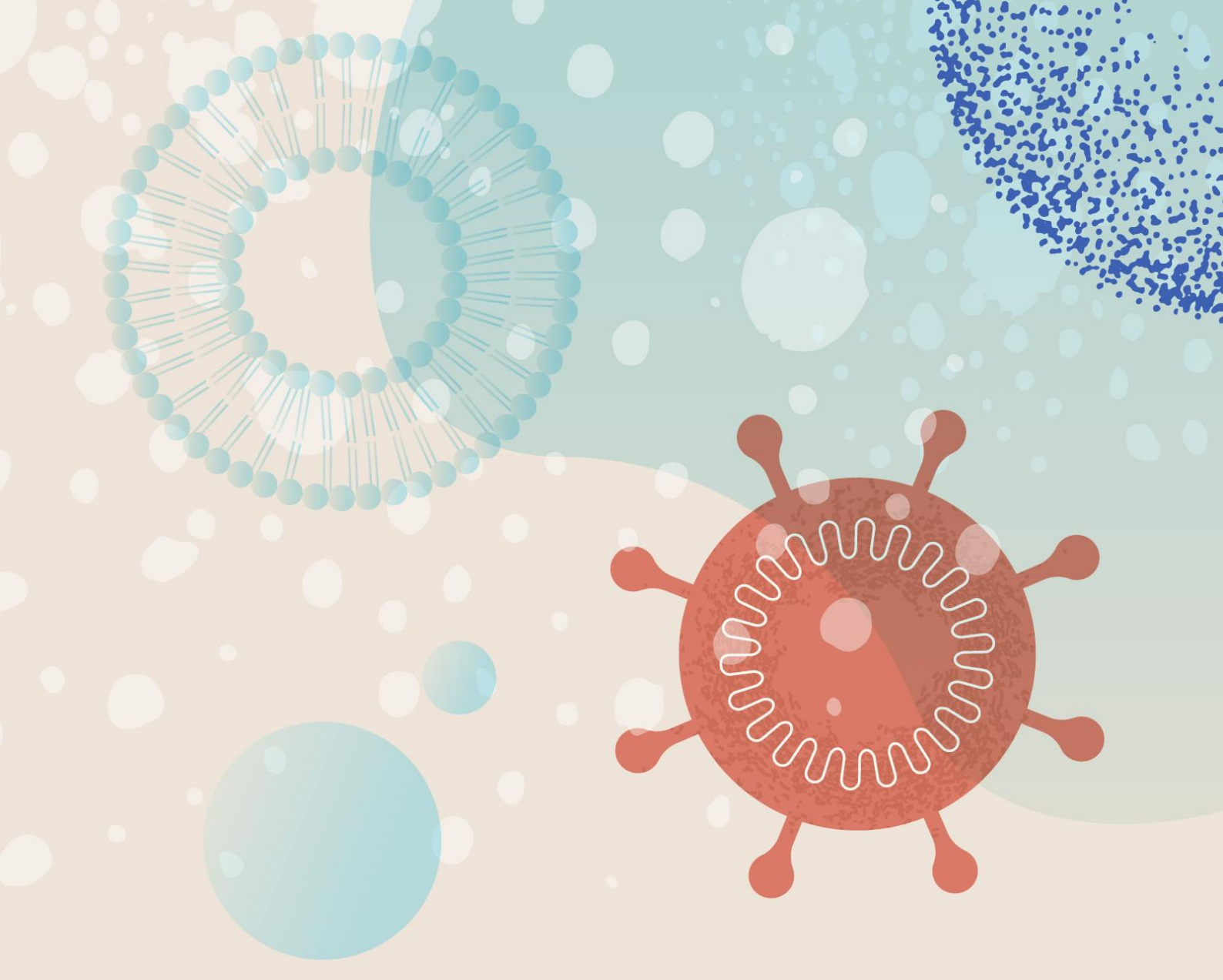

Guidance on an adapted Evidence to Recommendation Process for National Immunization Technical Advisory Groups

World Health Organization
European Region

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Content

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AEFI	Adverse event following immunization
CEA	cost–effectiveness analyses
CIN	cervical intraepithelial neoplasia
EtR Process	Evidence to Recommendation Process
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MoH	ministry of health
HPV	human papillomavirus
NITAG	National Immunization Technical Advisory Group
PCV	pneumococcal conjugate vaccine
RVGE	rotavirus gastroenteritis
SAGE	Strategic Advisory Group of Experts on Immunization
WG	working group

Glossary

Comparison	The comparison refers to the (existing) standard of care or other prevention measures (e.g. another vaccine) to which the new intervention is compared. In a PICO question, for the systematic collection of the evidence on benefits and harms, the comparison refers to the action to which the intervention is compared to in the studies. This can be a placebo, no vaccination or a vaccine not directed at the disease.
Consequences	Overall effects of an intervention. These effects can be advantageous or disadvantageous. The advantageous and disadvantageous consequences of an intervention should be balanced when developing a recommendation.
Criterion	Main issue that should be considered when developing a recommendation
Elements	Different types of data, that guide the collection of the evidence on the respective factor
Evidence	Available body of facts or information used to develop and support a recommendation. Evidence can derive from different sources including data from studies, surveillance activities and/or reports.
Factors	Different aspects of a criterion
Goal	Intended effect of the implementation of an intervention in a specific target population

GRADE	Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a rigorous method of assessing the certainty in evidence and the strength of recommendations in health care.
GRADE tables	Summary of the quality assessments of evidence using the GRADE method. In the context of recommendation-making the quality of the evidence should be systematically assessed for the evidence on benefits and harms of the intervention. When the NITAG collects evidence on benefits and harms of the intervention from systematic literature reviews, conducted for example by SAGE, the quality assessments from the GRADE tables developed by SAGE can be used.
Intervention	Vaccine, vaccine dosage, formulation and/or schedule considered for implementation
Options of intervention	Different vaccines, vaccine dosages, formulations and/or schedules that may be available and discussed by the NITAG
Outcomes	In the context of this guidance outcomes refer to the anticipated desirable and undesirable effects of an intervention, also called benefits and harms. These effects can be direct or indirect. Desirable outcomes relate to the efficacy, effectiveness, immunogenicity, impact or duration of protection of an intervention to prevent certain effects of an infection such as disease, severe disease, hospitalization, death. Undesirable outcomes relate to the safety of an intervention.
Policy question	Structured question the NITAG develops a recommendation for. The policy question should include the intervention under discussion, the population targeted by the intervention and the goal that should be achieved by the intervention. The policy question may include a comparison of the intervention or different options of intervention.

Population	In a policy question, the population refers to the group targeted for an intervention, that is the population that receives an intervention (e.g. children < 1 year of age to be vaccinated with rotavirus vaccine) and the population that experiences the effect of the intervention (e.g. children < 5 years of age indirectly protected by rotavirus vaccination of infants). In a PICO question on benefits and harms, the population refers to the group of people (age, sex, immune status, geography) for which the NITAG/working group/Secretariat considers it appropriate to assess the evidence on benefits and/or harms of an intervention. The PICO populations can be different for the different outcomes of interest (e.g. efficacy, effectiveness, duration of protection, impact).
Quality of evidence	Reliability, meaning completeness, transferability, bias of the collected information or data. For the evidence on benefits and harms of an intervention, the quality refers to the systematically assessed confidence that the collected evidence reflects the true effect.
Stakeholders	Generic term for people with interest in or concern about the implementation of the intervention, such as professional societies, liaison organizations, service providers, pharmaceutical companies, advocacy groups and the general public. Stakeholders may differ with the intervention under consideration.
Target population	The population that will receive the vaccine, but also their caregivers and/or other groups indirectly affected by the intervention.

Introduction

Purpose

This guidance describes a systematic approach called the "Evidence to Recommendation Process" (henceforth called "EtR Process") for use by national immunization technical advisory groups (NITAGs). The process described is based on the EtR Process used by the WHO Strategic Advisory Groups of Experts on Immunization (SAGE) and other long-functioning NITAGs, but has been adapted to fit the level of maturity of recently established NITAGs, which often face limited human and financial resources. Conducting a systematic literature review to collect evidence on the benefits and harms of an intervention is intentionally *not* included in the EtR Process described in this guidance. Instead NITAGs with limited time and resources are encouraged to use systematic literature reviews conducted by WHO SAGE or other long-functioning NITAGs as an evidence resource.

Intended audience

This document is intended as a guide for NITAG members, the Secretariat and experts involved in the development of recommendations on the vaccination policy of NITAGs that do not yet apply an EtR Process as used by SAGE, due to limited personnel and financial resources.

Overview and rationale of EtR Process

WHO recommends the use of a systematic process for the development of evidence-based recommendations for immunization policy. Evidence-based methods that systematically synthesize high-quality evidence were first used in clinical medicine and are considered best practice. These methods as applied to public health are defined as the "integration of the best available evidence with the knowledge and considered judgements from stakeholders and experts to benefit the needs of a population" (*1*).

The use of a systematic, standardized decision-making process such as the EtR Process ensures that NITAG deliberations consider a standard set of criteria and factors, and are consistent, transparent and well-documented. This approach will ensure that NITAG recommendations and corresponding ministry of health (MoH) decisions on introducing new vaccines or adapting existing programmes are based on the best available evidence.

Disclaimer

This guidance was developed using available materials from the Advisory Committee on Immunization Practices (ACIP), the German NITAG STIKO, the Joint Committee on Vaccine and Immunization (JCVI), WHO and WHO Strategic Advisory Group of Experts on Immunization (SAGE).

The Evidence to Recommendation Process

The EtR Process set out in this guidance describes a systematic approach that begins with developing country-specific Criteria Tables and ends with developing a recommendation.

The general EtR Process is composed of four steps. When using the EtR Process for the first time, the NITAG should conduct a Prerequisite Step to develop two tools that will be used for the following parts of the EtR Process (Fig. 1). The Prerequisite Step should be conducted by the whole NITAG. This step is not part of the general EtR Process and once the tools have been established, the EtR process starts with Step 1.

The responsibility for each of the four steps in the EtR Process is determined by the NITAG Chair and/or Secretariat. Generally, steps 1, 2 and 3 should be conducted by the NITAG Secretariat or a working group (WG) established for this purpose, composed of selected NITAG members, representatives of the Secretariat and relevant experts. If a WG is not established, relevant experts should be engaged whenever additional expertise is needed. All NITAG members should be involved in Step 4. In this document, the term WG/Secretariat is used to indicate those responsible for steps 1, 2 and 3, with the understanding that each country will decide whether to involve a WG.

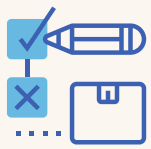
In the following pages, the Prerequisite Step and each of the four steps of the general EtR Process are described in detail and the output of the respective steps is summarized. To facilitate understanding of the EtR Process, examples from SAGE or other NITAG recommendations are provided. Usually NITAGs deal with policy questions concerning the implementation of new vaccines. Therefore, the guidance and provided examples focus mainly on these types of policy questions. However, the EtR Process can also be used to develop recommendations where different options of an intervention are available, such as different vaccine dosages, formulations and/or schedules.

Fig. 1. Evidence to Recommendation Process

PREREQUISITE STEP*

Generic Criteria Tables & EtR Framework

- **Generic Criteria Tables**
  Identify generic criteria, factors and elements for making NITAG recommendations
- **EtR Framework**
  Adapt EtR Framework template according to the NITAG's Generic Criteria Tables



* this step only needs to be conducted once

STEP 1

The policy question

- **Formulate policy question**
- **Structure policy question including:**
  - *Intervention under consideration*
  - *Population targeted by the intervention*
  - *Goal of the intervention*
- **If appropriate, include:**
  - Options and/or comparison of the intervention

STEP 2

The elements to consider

- **Make the elements specific**
- **Select the factors and specified elements** pertinent to the policy question

STEP 3

The evidence

- **Collect the evidence and consider the quality of the evidence** for the benefits and harms of the intervention
- **Synthesize the evidence** into the EtR Framework

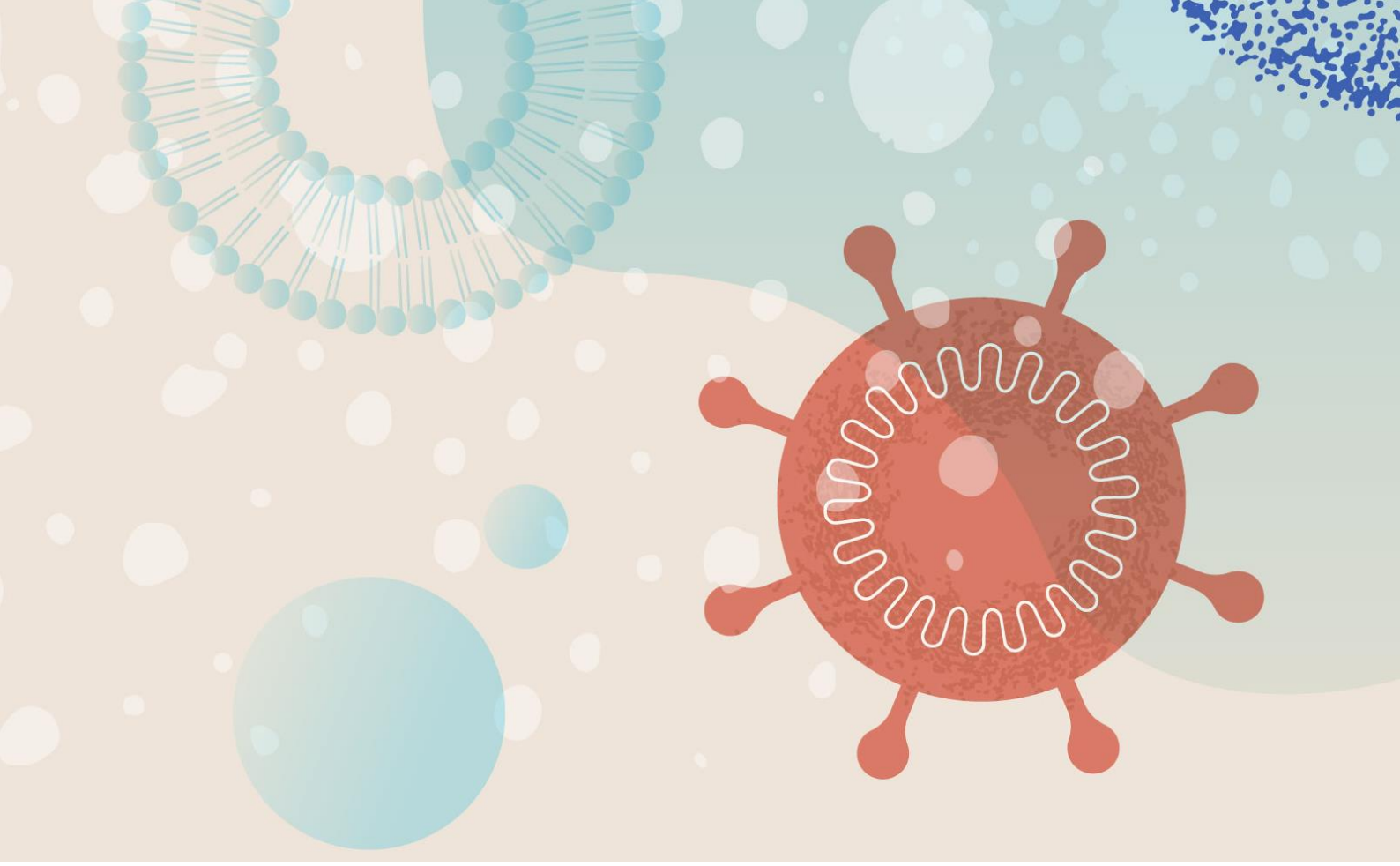
- **Balance the consequences**

STEP 4

The recommendation

- **Draft NITAG decision, recommendation and additional considerations**
- Discuss drafted NITAG decision, recommendation and additional considerations
- Vote or come to consensus on **final NITAG decision, recommendation and additional considerations**
- Prepare policy brief for ministry of health

NITAG Recommendation



Prerequisite Step:

Develop Generic Criteria Tables and the EtR Framework

Before embarking on the general EtR Process, NITAGs should first establish two tools: the **Generic Criteria Tables** and an **EtR Framework**. The task of establishing these tools is presented as a Prerequisite Step of the EtR Process. Once the tools are established, they should be included in the NITAG's standard operating procedures and used to complete the general EtR Process (steps 1-4) for any immunization-related question the NITAG is addressing. These tools ensure that the NITAG process of making evidence-based immunization recommendations is consistent, systematic and transparent, and allows the comparison of developed recommendations. The Generic Criteria Tables ensure that all aspects relevant for a NITAG's recommendation-making are addressed during the process, whereas the EtR Framework facilitates the summary and synthesis of the evidence supporting the NITAG's recommendation.

Appendix 1 provides a template for Generic Criteria Tables and Appendix 2 a template for an EtR Framework. Both these templates were developed based on those used by WHO SAGE and long-functioning NITAGs (Advisory Committee on Immunization Practices (ACIP), STIKO). NITAGs may adapt the provided templates or develop these tools by themselves.

Generic Criteria Tables

It is important that NITAGs consider all issues relevant for recommendation-making. Generic Criteria Tables as provided in Appendix 1 are useful as they contain all aspects that could be relevant for addressing any immunization policy question and for making immunization recommendations. To be suitable for any new NITAG recommendation, the aspects in the tables should be *generic*, meaning general and unspecific to any particular disease or vaccine, and *comprehensive*, meaning relevant for any vaccine policy question.

The Generic Criteria Tables in Appendix 1 were developed based on the experience and best practices of WHO SAGE and long-functioning NITAGs and should be suitable for the majority of NITAGs.

Based on the seven criteria listed in the SAGE EtR Framework, the Generic Criteria Tables comprise seven tables that link each of the seven criteria from the EtR Framework with a list of factors that address the different aspects of the specific criterion (Table 1). For example, for the criterion "Problem", the factors include among others "Burden/epidemiology of disease" and "Clinical characteristics of the disease". To guide the collection of evidence for each factor, one or more elements are listed, which describe the type of evidence. For example, the factor "Burden/epidemiology of disease" is composed of several elements, including frequency, severity and social impact of the disease. The factor "Clinical characteristics of the disease" is composed of elements such as signs and symptoms of disease, long-term complications of disease, and medical management of disease (Table 2). The extent to which each criterion should be addressed to guide the collection of evidence in a specific recommendation process varies according to the disease and vaccine under consideration and will be discussed in Step 2.

Table 1. Generic Criteria and linked Factors

Criterion	Factors
Criterion 1: **Problem**	• Burden/epidemiology of disease • Clinical characteristics of the disease • Use and Costs of Health Care • Alternative preventive and control measures • Regional and international considerations
Criterion 2: **Benefits and harms of the intervention**	• Efficacy and effectiveness of the intervention (benefits) • Safety of the intervention (harms) • Indirect effects of the intervention
Criterion 3: **Values and preferences of the target population**	• Perception of target population of the intervention and the disease • Differences by subgroups of target population • Demand
Criterion 4: **Acceptibility to stakeholders**	• Acceptability of the intervention • Financial, ethical and programmatic considerations
Criterion 5: **Resources use**	• Resource use and cost related to the intervention • Socioeconomic • Economic impact of intervention on immunization programme and health sector
Critieron 6: **Equity**	• Access to intervention • Ethics, legality of the intervention • Stigma
Criteiron 7: **Feasibility**	• Vaccine characteristics • Accessibility • Resources for storage, distribution • Information management • Disease and AEFI surveillance • Global, regional, local experiences • Vaccine availability

AEFI = adverse event following immunization

Table 2. Generic Criteria Table for Criterion 1: Problem

Criterion 1: **Problem**	
Factors	**Elements**
1.1 Burden/ epidemiology of disease	• Frequency of the disease (e.g. incidence, prevalence, secular trends) including in different sociodemographic and age groups • Severity of the disease (e.g. mortality, morbidity) including in different socio-demographic and age groups • Social impact of the disease (e.g. hospitalization rate, school and work sickness absenteeism, effects on high-risk groups and vulnerable populations) • Serogroup or serotype distribution (for serogroup- or serotype-specific vaccines)
1.2 Clinical characteristics of the disease	• Signs and symptoms of disease, severe forms of disease • Long-term complications of disease • Medical management of disease
1.3 Use and costs of health care	• Primary/secondary/tertiary care implications • Short- and long-term use of health care (e.g. treatments, hospitalization)
1.4 Alternative preventive and control measures	• Alternative preventive and control measures (e.g. health education, hygiene) and their effectiveness, costs and practicality
1.5 Regional and international considerations	• International burden of disease • Disease potential for international spread, and epidemic and pandemic risk

NITAGs or Secretariats should develop their own country-specific Generic Criteria Tables. They may use the provided template as a point of departure. Keeping the seven criteria from the suggested template, as all seven are important for recommendation- and decision-making and make NITAG recommendations on different topics compatible, the NITAG can adapt the template to fit the country context by:

a) Aligning the terms used to describe the criteria, factors and elements with commonly used terms in the country.

b) Regrouping factors and elements under other criteria if found to be more appropriate.

c) Including only those factors and elements in the Generic Criteria Table that the NITAG considers appropriate for making recommendations. Some NITAGs for example do not use cost-effectiveness data for recommendation-making because the MoH considers the financial aspects of an intervention at later stages of the decision-making process. These NITAGs may choose to omit the factors and elements related to cost-effectiveness when adopting the Generic Criteria Tables. NITAGs should be aware that some factors and elements might not be important for one policy question but can be for another. So, factors and elements should only be omitted with caution.

Evidence to Recommendation Framework

SAGE and long-functioning NITAGs use an EtR Framework each time they develop a recommendation to summarize and synthesize the evidence supporting their recommendations. Such an EtR Framework provides a structure that shows the logical progression from the evidence to the decision of whether to recommend the intervention and explains the rationale behind the decision. It is therefore a useful tool for NITAGs, WGs and/or Secretariats. The EtR Framework template found in Appendix 2 comprises the following sections:

1. Summary of Evidence to Recommendation (see also Table 3)

- The **"Introduction" section** presents the policy question that is the topic of the EtR Framework and the background of the policy question.

- The **"Criteria" section** is composed of rows delineating the seven criteria that are important to consider for developing any NITAG recommendation. They are aligned with the seven criteria of the Generic Criteria Tables. There are one or more questions on each criterion, options for answering the question, and space to summarize the supporting evidence. The factors and elements from the respective criterion table help to define evidence that should be collected to answer the question(s). The "Criteria" section is followed by a row on the balance of all advantageous and disadvantageous and desirable consequences of the intervention.

- The section **"Draft NITAG Recommendation Developed by WG/Secretariat"** includes the draft NITAG decision, the text of the draft recommendation, and an optional line for additional considerations.

2. Final Deliberation and Decision by the NITAG

This section presents the results of NITAG deliberation on the section "1. Summary of Evidence to Recommendation" and the final recommendation, with additional considerations as needed.

The EtR Framework template can be used by NITAGs to develop their own EtR Framework. If the NITAG adapted the Generic Criteria Tables from Appendix 1 (e.g. by rephrasing or regrouping elements and/or factors) the EtR Framework template should be adapted accordingly.

Note: The EtR Framework as found in Appendix 2 is suitable for policy questions on the introduction of a new intervention if no comparable intervention is in place. Sometimes NITAGs address policy questions that compare the intervention with the existing prevention measures or with different intervention options (e.g. different vaccine formulations, dosages, schedules). In such cases, the phrasing of the questions and the judgements from the EtR Framework may need further adaptation to reflect the comparison of two interventions (existing and new vaccine) or possible options. Examples of EtR Frameworks developed by SAGE for different policy questions and interventions, including on different options of intervention, can be found on the WHO website (*2*).

The use of these tools for completing step 1-4 is described below.

Table 3. EtR Framework – Summary of Evidence to Recommendation

Introduction
Specific policy question: • Specific intervention • Population targeted for the intervention • Goal that should be reached by the introduction of the intervention in the target group
Background:

Criteria			
Criterion	**Criteria questions and WG/Secretariat judgements**	**Summary of evidence**	**Additional information**
1. Problem			
2. Benefits and harms of the intervention			
3. Values and preferences of the target population			
4. Acceptability to stakeholders			
5. Resource use			
6. Equity			
7. Feasibility			
Balance of consequences of intervention			

Draft NITAG recommendation developed by WG/Secretariat	
Draft NITAG decision	
Draft recommendation	
Additional considerations	

The use of these tools for completing steps 1–4 is described below.

Outputs of the Prerequisite Step

- ✓ Set of comprehensive criteria (Generic Criteria Tables) adapted to the country's context for use in starting the EtR Process
- ✓ EtR Framework aligned with the Generic Criteria Tables
- ✓ Finalized Generic Criteria Tables and EtR Framework included as part of the NITAG standard operating procedures

Step 1

The Policy Question

The EtR Process relies upon the formulation of a clear policy question, which is either raised by the MoH and addressed to the NITAG or raised by the NITAG itself. The initial policy question is usually rather broad. For example, the question may ask:

- Should vaccine X be introduced in a routine vaccination programme?
- Should vaccine X be introduced for only a particular group of people?
- Should the schedule of vaccine X be reviewed?

The purpose of Step 1 is to provide structure to the broad policy question to guide the collection of evidence. The following aspects should be included in the structured policy question:

Box 1. Examples of structured policy questions

- Should two doses of an HPV vaccine be given to girls between 9-14 years of age to reduce HPV infections and HPV-associated cancers? (STIKO, 2014)
- Should rotavirus vaccine be recommended, to be administered to infants (<6 months of age) to reduce the number of rotavirus infections requiring hospital admission in children <5 years of age? (STIKO, 2013)
- Should adolescents aged 12-15 years receive COVID-19 vaccination with a vaccine licensed for this age group?
- Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date? (ACIP, 2019) .

HPV = human papillomavirus;
PCV = pneumococcal conjugate vaccine

- **Intervention.** Usually the intervention refers to a new vaccine that is considered for introduction. The NITAG should specify the vaccine formulation, dosage and schedule. The intervention may also refer to a new vaccine, vaccine schedule, formulation or dosage that is to replace an existing vaccine, schedule, formulation or dosage.

- **Population.** The population targeted to receive the intervention and/or that will be affected by a change or the new introduction of an intervention.

- **Goal of intervention.** The goal that should be reached with the introduction of the intervention within the target population should be outlined. The goal might be a measurable goal (e.g. reduction of a certain disease) to allow for later evaluation of the impact of the recommendation, but not necessarily.

Box 1 provides some examples of structured policy questions from NITAGs.

In addition, some policy questions may also include a comparison or different options.

- **Comparison.** If the NITAG compares a new intervention to an existing one, the policy question may include a comparison (e.g. a new formulation, dosage and/or schedule of the existing vaccine). If the new intervention is simply compared to "no vaccination" or other existing preventive measures in place, the comparison does not need to be indicated in the policy question.

- **Options.** If several options of an intervention are available (e.g. different vaccine formulations, dosages or schedules) and the NITAG discusses which of these options should be implemented, the policy question may include the different options.

Box 2. Examples of structured policy questions including comparison or options

- Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different? (SAGE, 2017)

- How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection? (SAGE, 2017)

IPD = invasive pneumococcal disease

Box 2 provides some examples of structured policy questions with comparison or options

Note: Sometimes the NITAG may discuss whether or not to implement a certain intervention and at the same time discuss whether the intervention should be recommended to all or only to specific groups (e.g. particular at-risk groups). These are actually two policy questions (not two options or a comparison). Therefore, recommendations on these questions should be separately developed and the evidence be summarized in separate EtR Frameworks (e.g. Policy question 1: Should influenza vaccination be recommended for children? Policy question 2: Should influenza vaccination be recommended for all children or only for children at risk for severe disease or those in contact with people at risk for severe disease?).

Synthesis into EtR Framework

The structured policy question should be stated in the "Introduction" section of the EtR Framework (see Table 3 and Appendix 2). The NITAG should provide a definition of the different aspects of the policy question.

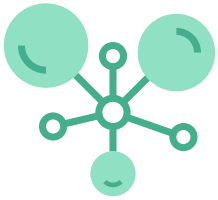
A brief summary of information needed to understand the policy question and the importance of the recommendation should be put in the "Background" section of the Introduction. If the recommendation would be for "off-label use" (i.e. an indication not specified in the label approved by the national regulatory authority), this should be clearly stated in the background.

Outputs of Step 1

- ✓ A structured policy question, defining the intervention under consideration, the population and the vaccination goal
- ✓ The structured policy question and background recorded in the “Introduction” section of the EtR Framework

Step 2

The elements to consider



Since the factors that describe the different aspects of the criterion and the elements that guide the collection of evidence (as they are listed in the NITAG's Generic Criteria Tables) are comprehensive and broad, some may not be specific enough or sufficiently relevant to address the current policy question. The purpose of Step 2 is to develop a list of factors and elements customized to the policy question by a) making them specific to the respective disease, intervention and population and b) selecting only those that are relevant to the policy question.

a) Make the elements specific

The WG/Secretariat should develop criteria tables that are specific to the disease, intervention and population under consideration. To do so, the elements listed in the Generic Criteria Tables should be specified for the disease, intervention and population under consideration. If some elements or factors are not applicable, these might dropped from the table. For example WGs/Secretariats addressing a policy question on measles vaccine may drop the element "1.1 Serotype distribution" as it is not applicable, because the measles virus has only one serotype.

With regard to the later collection of evidence, the definition of the "population" from the policy question may not be suitable for all criteria. For example, for the collection of evidence on the burden of disease, the "population" may include all age groups and sexes; for the benefits and harms of the intervention the "population" may include only certain age groups and sexes targeted for vaccination; for the values and preferences the "population" may include people targeted for vaccination as well as their care-givers and parts of the population that are impacted by the intervention. The WG/Secretariat may adapt the definition of the "population" where needed, to fit the criterion.

Table 4 provides an example of specified elements that were considered by a NITAG for the factor on burden/epidemiology of HPV in girls.

Table 4: Example of specified elements on burden/epidemiology of HPV in girls

Criterion 1: **Problem**	
Factors	**Specified elements**
1.1 Burden/epidemiology of disease	• Incidence and/or prevalence of HPV infections, anogenital warts/condyloma, cervical precancer, cervical cancer, oropharyngeal cancer, anal cancer, vaginal/vulvar cancer • Mortality of cervical cancer, oropharyngeal cancer

b) Select the factors and specified elements relevant for the policy question (population, intervention, goal)

Not all specified elements and factors may be relevant to developing recommendations on the structured policy question. Therefore, the WG/Secretariat should review the criteria tables and select only those factors and specified elements they are relevant for the disease, intervention and population under consideration to collect evidence on. Elements not applicable to the disease, intervention and population under consideration were dropped from the tables as part of step "a". The number of selected factors and elements might vary across different criteria. The factors and elements listed with Criterion 1 "Problem" are relevant for most of the policy questions, while only some of the factors and elements listed with criteria 3-7 may be deemed relevant for the specific policy question. For example, for a policy question on pneumococcal vaccines, factor 6.3 "Stigma", may not be relevant since there may be no stigma associated with the disease or intervention and it might therefore not be selected and not included in the specific list.

Outputs of Step 2

- ✓ Criteria tables specific to the policy question including selected factors and specified elements that will guide the collection of evidence upon which the NITAG's recommendation-making will be based.

Step 3

The evidence

This step centres on the evidence upon which the WG/Secretariat will base its draft recommendation. The purpose of Step 3 is to collect evidence on the selected factors and specified elements determined in Step 2, consider the quality of this evidence on the benefits and harms of the intervention, and synthesize the evidence and balance the consequences of the intervention based on all gathered evidence. As such, it is the most labour-intensive part of the EtR Process. Therefore, WGs/Secretariats should allow sufficient time and resources. If additional expertise is needed for this task, relevant experts should be engaged.

Below the substeps of Step 3 are summarized and addressed in more detail for each of the seven criteria.

Collection of Evidence

Evidence should be gathered for all selected specified elements. If the NITAG compares a new intervention with an existing one or considers different available options of a new intervention, evidence needs to be gathered both for the intervention and the comparison or the options discussed.

Evidence can be gathered from many different sources, that in turn depend upon the criterion and element. Some evidence may be obtained from literature (published or unpublished), statistical data or surveillance records. Other critical evidence may be obtained from documents/publications and/or recommendations from WHO, WHO SAGE, Regional Immunization Technical Advisory Groups (RITAGs) such as the European Technical Advisory Group of Experts on Immunization (ETAGE) or other NITAGs. Experiences from countries that have already implemented the discussed intervention might be valuable resources for the WG/Secretariat to take into account. To collect evidence on factors and elements of Criterion 2 "Benefits and harms of the intervention" SAGE and some NITAGs conduct systematic literature reviews. As this criterion refers to the desirable and undesirable effects of the intervention, called the "outcomes", it is critical for developing recommendations. Conducting a systematic literature review is very time and resource consuming and should only be done if the necessary capacities are available. Otherwise the WG/Secretariat may use the systematic literature reviews on the benefits and harms of the intervention conducted by others (see further detail on Criterion 2 below).

The NITAG Resource Centre provides various documents relevant for NITAGs including published recommendations from different NITAGs and SAGE (*3*), as well as a registry on systematic reviews on immunization topics (SYSVAC) (*4*).

If for some factors and/or elements, evidence is not available and/or data from other countries is not transferable to the countries' situation, the WG/Secretariat may decide to conduct their own studies, surveys or (systematic) literature reviews to obtain evidence on elements pertinent to their policy question. The time and resources needed to develop such evidence should be considered.

Although the evidence collected may be the best available, some might be incomplete or biased. Since the evidence supports a later recommendation, the quality of the collected evidence should be considered. This point is especially important for the evidence collected on Criterion 2 "Benefits and harms of the intervention". Therefore, those who conduct systematic reviews on the benefits and harms of the intervention use systematic methods, (e.g. GRADE (*5*)) , to assess the quality of evidence, which determines the level of confidence they have that the effects reported in the collected evidence reflect or are close to the true effects. WHO SAGE also conducts GRADE quality assessments of evidence when they consider recommendations on immunization policy. The results of SAGE assessments for specific vaccines are summarized in Evidence Profiles which can be found on the WHO website along with the vaccine position papers (*2*) and in the SAGE background documents. When the WG/Secretariat uses the systematic reviews on benefits and harms of the intervention conducted by SAGE or others, they should use the quality assessments from these reviews to summarize and synthesize the evidence in the corresponding part of the EtR Framework for Criterion 2.

For the evidence collected on the other criteria, its quality shall be considered with regards to its reliability (i.e., completeness, transferability, bias). Surveillance data for example, may be prone to underestimating the burden of disease if there is a lack of laboratory confirmation, poor access to health care, incomplete reporting, or the absence of or incomplete disease registries, including cancer registries. Incompleteness or bias can lead to the significance of the problem or other criteria being either overlooked or exaggerated, which in turn may lead to an inappropriate recommendation. The WHO "*Guidance for the development of evidence-based vaccination-related recommendations*" (*6*) provides several tools for identification of evidence limitations that WGs/Secretariats may use. If in doubt about the reliability of the evidence collected within the country, the WG/Secretariat may consider using other sources of evidence (e.g. estimates from WHO or from other countries) and/or should clearly point out the limitations of the national evidence. The NITAG's recommendation may indicate the need for further evidence to make a final decision.

Note: Lower quality data does not mean that the recommendation cannot be made, but the limitations should be outlined and taken into account when developing the recommendation.

Synthesis into the EtR Framework

Synthesis in this step refers to the process of making evidence-based judgements on criteria questions and summarizing the evidence and information that informed the judgements. This synthesis should be done in the "Criteria" section of the EtR Framework (Table 5).

Table 5: EtR Framework - Criteria section

Criterion		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
For each of the seven criteria for which evidence has been collected, the WG/Secretariat should answer or make a judgement on the questions provided. Judgements on each question are summarized as checkboxes. In most cases, the judgements will be made by the WG/Secretariat who prepare the EtR Framework. The judgements should be a result of the WG/Secretariat reaching a consensus; however, minority opinions expressed during the discussion should be captured in the "additional information" column.	*The evidence used to inform each of the WG/Secretariat's judgements made in column 1 should be summarized. If published evidence is available, a paragraph or bulleted list summarizing the important considerations is sufficient, with mention of the most critical references or links to more detailed summaries of the evidence. If no peer-reviewed body of evidence is available, this should be simply stated, and any additional information used to inform the judgement indicated. The intent is to be transparent about the information that was used to make the judgement.*	*Other data, information or even assumptions and logic used to inform or justify a judgement may be provided. WGs/Secretariats may make different judgements for one or more subgroups in relation to some or all criteria. Subgroups to consider depend on the policy questions but could include people who are older or groups that may especially benefit from the intervention or that may have higher risk of adverse events. When relevant, the WG/Secretariat may also report additional details, such as dissenting views of WG/Secretariat members or the results of voting on judgements where there was disagreement. Minority opinions voiced during discussions should be presented to increase transparency around the deliberation process.*

Examples of EtR Frameworks developed by SAGE for different policy questions and interventions can be found on the WHO website (*2*). Examples of EtR Frameworks developed by ACIP on different interventions can be found on the Centers for Disease Control and Prevention website.[7]

In the following, guidance for completing Step 3 is given for each of the criteria.

Criterion 1

Problem

The problem in this sense means the disease or other public health problem. This criterion aims to determine whether the problem is of public health importance and to what extent.

Collection of evidence

In most cases, evidence on the problem includes the burden/epidemiology of disease. Local or national surveillance data, studies and/or statistical data have the advantage of being most relevant to the country context. However, in some cases, evidence from other countries would be relevant to consider (e.g. for recommendations on vaccines against diseases that have already been eliminated or eradicated from a country and may be prone to national importation or international disease spread, such as measles, polio, or diphtheria, or for travel vaccines). If data from local sources are not available, data from WHO regional- and country-specific estimates may be consulted, and are conveniently available on the WHO website. The evidence on disease burden from countries with similar demographic or socioeconomic conditions may also be used as proxy evidence. Mathematical models may provide evidence on hypothetical situations but require relevant expertise and time, and may be expensive to conduct. If possible, evidence on burden of disease should include frequency of disease by agegroups, gender or socio-demographics.

Synthesis into EtR Framework

- Criterion question "Is the problem of public health importance?"
  A judgement should be made using one of the provided answers in the "Criteria" section of the EtR Framework (Appendix 2). The available scientific evidence supporting the judgement should be summarized.

If evidence is not available, expert opinion on the public importance of the problem should be provided. Any additional considerations, including whether there are disadvantaged groups disproportionately affected by the problem should be identified. If the WG/Secretariat identified any issues regarding the quality of the evidence (i.e. transferability, completeness and/or bias) these may be indicated.

Criterion 2

Benefits and harms of the intervention

"Benefits and harms of the intervention" is a key criterion because it describes and compares the various desirable and undesirable effects, called "outcomes", of the intervention. "Benefits" refer to the desirable outcomes of the intervention, meaning the efficacy and effectiveness of an intervention (e.g. against a certain disease, infection with a pathogen, hospitalization or death due to a disease and/or the duration of protection of an intervention). The "harms" refer to the anticipated undesirable outcomes, addressing the overall safety of an intervention, (e.g. adverse events following immunization). The fact that a vaccine is administered to healthy people to prevent disease means that the tolerance for adverse events is very low (*8*). Therefore, WGs/Secretariats should seek high-quality evidence on benefits and harms to support a recommendation.

Collection of evidence

To collect high-quality evidence on the benefits and harms of an intervention, WHO SAGE conducts a systematic literature review on efficacy/ effectiveness, safety and duration of protection for each intervention that it considers. A summary of the evidence collected through the systematic review can be found in WHO position papers[2] and SAGE background documents. Other bodies, including some NITAGs, also conduct systematic reviews. Some of these have recently been compiled into a database called SYSVAC that is accessible through the NITAG Resource Center (*3*, *4*). Conducting a systematic literature review is a very resource consuming process. Therefore, if the resources are not available, the WG/Secretariat may use the systematic reviews conducted by WHO SAGE or other NITAGs to collect the evidence on benefits and harms.

A systematic literature review starts with developing one or more so called "PICO questions", which predefine the Population, Intervention, Comparison and Outcomes. The PICO question facilitates the literature search and focusses it on the defined components. The concept of PICO is explained in more detail in Appendix 3.

NITAGs may decide to conduct their own systematic literature review, for example, if there are no such reviews available on the benefits and harms of the specific intervention, or the available reviews are not suitable. In such cases the WG/Secretariat should start by developing one or more PICO questions. A PICO question may also be developed and used to select the most appropriate literature review conducted by others – if several literature reviews on benefits and harms of the intervention are available.

PICO specifies, among other things, the desirable and undesirable outcomes of an intervention (e.g. prevention outcomes or adverse effects) that are considered critical and important for recommendation-making (see also explanation in Appendix 3). If the NITAG uses literature reviews conducted by SAGE or other NITAGs, the PICO outcomes considered in the literature review may differ from the elements the WG/Secretariat has specified and selected for Criterion 2 (see Step 2 of the EtR Process). In this case, the WG/Secretariat should discuss whether and why the elements they have specified are still considered relevant for their recommendation and may decide to obtain evidence on these elements from other systematic reviews or other sources. If no evidence can be obtained for the specified elements, the WG/Secretariat may decide to conduct their own systematic review or collect expert opinions from NITAG members or external experts, or indicate the lack of evidence on these elements in their recommendation. As different subgroups, such as age or at-risk groups may be affected differently by the disease and/or intervention, the desirable and undesirable outcomes of the intervention may also differ in different subgroups. If information is available for outcomes in subgroups, the WG/Secretariat may take these into account.

Considering the quality of the evidence

As mentioned above, the quality of the evidence collected on "Benefits and harms of the intervention" is especially important. The quality determines the overall certainty and confidence that the effects of the intervention reported in the collected evidence reflect the true outcomes. Those conducting systematic reviews should therefore systematically assess the quality of the evidence (e.g. using GRADE (*5*)). The GRADE approach provides a framework to up- and downgrade the rating of the quality of the evidence, based on methodological and quantitative assessments (*6*). WHO SAGE uses the GRADE method and summarizes the results of their GRADE quality assessments in the Evidence Profiles, which can be found on the WHO website along with the vaccine position papers and in the SAGE background documents. If the WG/Secretariat uses systematic literature reviews conducted by SAGE or other NITAGs to collect the evidence on benefits and harms, they may use the results of the quality assessment from the considered systematic reviews to indicate their certainty or confidence in the evidence. Tables 6.1 and 6.2 provide examples of GRADE tables that SAGE developed on the efficacy and safety of HPV vaccination in adolescent girls. If WGs/Secretariats conduct their own systematic reviews, they should evaluate the quality of the evidence as recommended in the Cochrane Handbook (*9*).

Note: The outcomes considered in the collection of evidence on the benefits and harms of an intervention are listed in the SAGE GRADE table ("Outcome") and can be found in the systematic review itself.

Table 6.1. SAGE GRADE Table on the efficacy of HPV vaccination in adolescent girls

Population : Adolescent girls
Intervention: Primary HPV vaccination
Comparison: Placebo/ no vaccination
Outcome : HPV infection

What is the scientific evidence to support administration of the currently licensed HPV vaccines to young adolescent girls, naïve to vaccine-related HPV types, to prevent cervical cancer later in life?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		8/ RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[2]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.**
	Conclusion			**We are moderately confident that administration of primary HPV vaccination to young adolescent girls prevents cervical cancer later in life.**

Source: WHO (*10*)

Table 6.2. SAGE GRADE table on the efficacy of HPV vaccination in adolescent girls

Population : Adolescent girls
Intervention: HPV vaccination
Comparison: Placebo/ no vaccination
Outcome : Severe adverse events following immunization

In immunocompetent adolescent girls who are naïve to vaccine-related HPV types, what is the (attributable) incidence of serious adverse events for any dose of HPV vaccination?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT[1] 2/ observational	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[2]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.**
	Conclusion			**We are moderately confident that the risk of severe adverse events following vaccination with any dose of HPV is low.**

Source: WHO (*11*)

Synthesis into EtR Framework

The outcomes identified from the systematic literature reviews or by the WG/Secretariat should be listed in the "Background" of the "Introduction section" of the EtR Framework.

Five criteria questions are presented for Criterion 2:

- Criterion question: "How substantial are the benefits of the intervention?"
  The evidence on the magnitude of the benefits of the intervention should be summarized. Benefits for the individual (e.g. vaccine efficacy and effectiveness, immunogenicity, duration of protection) should be distinguished from the benefits at the population level (e.g. herd immunity). The following aspects may also be addressed:

    - potential differences regarding the benefits across subgroups (by age, gender, pregnancy or lactation status, occupation (i.e. healthcare workers), immune status, race, socioeconomic status, and other groups);
    - other indirect benefits

- Criterion question: "How substantial are the harms of the intervention?"
  The evidence on the magnitude of the harms of the intervention both on the individual (e.g. adverse events following immunization) and/or at the population level (e.g. age-shift of disease, serotype replacement) should be summarized. Potential differences across subgroups regarding the harms should be taken into consideration. The WG/Secretariat may consider whether there should be separate recommendations for subgroups based on the harms of the intervention.

- Criterion question: "What is the balance between the benefits and harms of the intervention?"
  The WG/Secretariat should indicate the balance of the benefits and harms of the intervention under consideration compared to the existing intervention, which could be non-vaccination and standard care or an existing vaccine. If different available options of intervention are discussed, the benefits and harms of one option should be compared to those of the other option. The evidence on both the individual and population level that supports their judgement should be briefly summarized.

- Criterion question: "What is the overall quality of the evidence (meaning here: certainty/confidence) for the *benefits* (e.g., efficacy/effectiveness, immunogenicity)?"

and

- Criterion question: "What is the overall quality of the evidence (meaning here: certainty/confidence) for the harms (e.g., safety, age-shift of disease, changes in serotype-distribution)?"
  Because the quality of the evidence on benefits and harms of the intervention is critical, it should be indicated. If the WG/Secretariat uses literature reviews conducted by WHO SAGE and/or other NITAGs, the results of the quality assessment (e.g. GRADE evidence profiles) may be used. The WG/Secretariat may use the statement on the quality of evidence provided in the section "Summary of findings" of the GRADE evidence profile (see tables 6.1 and 6.2), to answer these criteria questions. The "final numerical rating of quality of evidence", nowadays often included in the statement, can be used to indicate the level of confidence.
  If GRADE was not used, the method and/or any other tools used to evaluate the quality of evidence should be described and the results indicated under "Additional information".

Note: If the WG/Secretariat conducted their own systematic literature review or considered additional elements for the benefits and harms addressed by other sources, the quality of the evidence for these elements should also be systematically assessed (e.g. using GRADE).

Criterion 3

Values and preferences of the target population

This criterion relates to the values and preferences of the target population with regard to the benefits and harms of the intervention. The target population may not only include people targeted for the intervention, but also their caregivers and/or other people indirectly effected by the intervention.

Collection of evidence

Sources of evidence may include both primary (published or unpublished) and secondary data. WGs/Secretariats may conduct a systematic or rapid literature review to identify local or national data, observational data, national surveys, or research studies on the topic. If evidence is limited, WG/Secretariat deliberations can be used.

Synthesis into EtR Framework

Two criteria questions are presented for Criterion 3 in the "Criteria" section of the EtR Framework. The sources of evidence used to support the judgements (e.g. targeted research, questionnaires, WG/Secretariat deliberations) should be transparently described.

- Criterion question: "Does the target population feel that the *benefits* of the intervention are large relative to the *harms* of the intervention?"

  Provide a summary of the evidence on the perspectives and perceptions about the disease and the intervention of the target population, including recipients of the intervention and their caregivers and/or other people indirectly affected by the intervention.

  Any measured perspectives and preferences of the target population with regard to the benefits of the intervention versus the potential harms, as well as the burden of disease prevented by the intervention, should be taken into consideration. If the target population does not value the intervention, or attributes little value to the benefits and harms of the intervention, potential education measures may be considered.

- Criterion question: "Is there important uncertainty about or variability in how people value the benefits and harms of the intervention?"
  If there is no evidence available on how the people value the benefits and harms, and therefore there is important uncertainty about this, such uncertainty should be indicated here. If such data is available and suggests important variability in how the target population value the intervention's effects, this variability should also be indicated. If evidence is limited, WG/Secretariat expert opinion can be used or in cases where an evaluation of people's perspectives, perceptions and preferences is deemed to be desirable and there is sufficient time, a systematic assessment of how the target group values the intervention may be considered.

Criterion 4

Acceptability to stakeholders

This criterion assesses the acceptability of the intervention to key stakeholders which may impact their buy-in and cooperation in implementation. Stakeholders, some of whom may be liaison members of the NITAG, may include members of professional societies, liaison organizations, service providers, pharmaceutical companies, advocacy groups, and the general public. As key stakeholders may differ depending on the intervention under discussion, the WG/Secretariat should define the stakeholders they consider for a specific recommendation.

Collection of evidence

Sources of evidence may include published formative research or surveys that may be found through a literature review. If no such evidence is available and there is enough time and resources, the WG/Secretariat may consider conducting a survey on the acceptability to stakeholders.

Synthesis into EtR Framework

The stakeholders considered by the WG/Secretariat during their discussion should be indicated in the "Summary of evidence" column in the "Criteria" section of the EtR Framework.

- Criterion question: "Is the intervention acceptable to key stakeholders?"
  If no published evidence is available, the judgement on this question may often represent the expert opinion of the WG/Secretariat. Liaison members of the NITAG can often provide a perspective for their organizations that may be useful in deliberations. The assessment of whether the intervention would be acceptable (ethically, programmatically, financially etc.) to these stakeholders should be summarized. If the acceptability of the intervention varies across the different stakeholder groups, this should be outlined and the rationale for it summarized. In cases where the WG/Secretariat discusses different options of an intervention, possible differences in the acceptability to stakeholders of the different options may be considered. The WG/Secretariat may also consider the acceptability of alternative prevention and control measures that are compared with the intervention.

Criterion 5

Resource use

NITAGs that take into account economic evaluations, may assess whether the discussed intervention (or the different options, if any) is cost-effective. The purpose of Criterion 5 is to consider the relative value of the intervention and identify additional factors that may affect its cost-effectiveness profile.

If possible, the WG/Secretariat should consult a health economist for collecting, evaluating, and synthesizing the evidence on the resource use.

Collection of evidence

Sources of evidence may include cost-effectiveness analyses (CEAs) conducted by independent researchers, the vaccine industry and local economists in the country or in other countries. The results from CEAs conducted in other countries may not always be transferrable to the country's context as the input parameters for the analysis may be different in different countries.

A CEA will generally be needed for new vaccines and new recommendations with major programmatic economic impact. If there are two or more studies, any major differences between the studies should be identified. Any other important factors that may affect the cost-effectiveness profile of the intervention should be listed.

NITAGs that take into account cost-effectiveness when making recommendations may consider the following questions when reviewing the evidence:

- What is the cost-effectiveness of the intervention?
- How does the cost-effectiveness of the intervention vary in sensitivity analysis?
- How does the cost-effectiveness change in response to changes in context, assumptions and/or model structure, across different studies, etc.?

Synthesis into EtR Framework

- Criterion question: "Is the intervention a reasonable and efficient allocation of resources?" Evidence supporting the judgement should be summarized. If several analyses are used the major differences in baseline assumptions should be outlined and the uncertainty of these analyses (if any) and possible variation of the results should be described.

Criterion 6

Equity

This criterion focuses on the impact of the intervention on health equity. Health inequities are differences in health considered unfair or unjust and that could have been avoided. This criterion facilitates transparent and explicit consideration of the impact of the intervention on the target population including when compared with the alternative preventive and control measures. Specifically, any groups or settings that would be disadvantaged as a result of the intervention should be identified.

Collection of evidence

Sources used may include any publications reporting on issues of health equity or inequity on the topic under consideration. Relevant studies may be qualitative or quantitative.

Synthesis into EtR Framework

- Criterion question: "What would be the impact of the intervention on health equity?"
  The WG/Secretariat should summarize the evidence that supports their judgement. This should include findings on issues of health inequities or identified groups who may be disadvantaged by the intervention (or the different options, if any), the problem, or the alternative preventive and control measures. Legal and ethical aspects should be included.

The WG/Secretariat may consider from the evidence the following questions and indicate their answers in the "Additional Information" column:

- Are there plausible reasons for anticipating differences in the relative efficacy/effectiveness of the intervention for disadvantaged groups or settings?
- Are there different baseline conditions across groups or settings that affect the absolute efficacy/effectiveness of the intervention or the importance of the problem for disadvantaged groups or settings?
- Are there important considerations that should be made when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?

If no evidence is identified and time and resources allow, the WG/Secretariat may consider initiating a study or survey on this criterion. Otherwise if evidence is limited this should be transparently stated. In that case, WGs/Secretariats should answer the above questions to the best of their ability.

Criterion 7

Feasibility

The purpose of Criterion 7 is to determine whether the intervention is feasible to implement. To do so the characteristics of the intervention (e.g. vaccine dosage, formulation, schedule, and flexibility of schedule) and any special storage requirements should be assessed.

The WG/Secretariat should consider the potential impact that the introduction of the intervention has on both the programme and the overall health system (e.g. if there are already serious weaknesses in the immunization programme, adding a new vaccine may cause additional burdens and worsen the programme's performance). Furthermore, the WG/Secretariat should consider whether the immunization programme and health system are capable of handling, storing and administering the additional vaccine adequately, and whether the current workforce is sufficient in number, adequately trained and motivated to handle the adding of a new vaccine. Other issues that the WG/Secretariat should consider include the capacity of the immunization information system to provide credible data on coverage of the new vaccine, including a breakdown by subnational level, which will be essential to monitor and evaluate the programme performance; and the feasibility of adding the new vaccine to the national vaccine safety monitoring system. Implementation issues are not expected to drive the recommendation, but it is possible that they may change the type of recommendation, influence the wording of the recommendation or at least inform additional considerations that may be added to the recommendation.

It is important that the WG/Secretariat is aware of the current and future supply situation and likely future trends. Introducing a vaccine with a limited global supply can present serious challenges for immunization programmes and the WG/Secretariat may consider delaying the introduction or adopting a phased introduction strategy until a healthier market develops.

Collection of evidence

Sources of evidence will most likely be input from pharmaceutical companies (characteristics of the intervention), from stakeholders or expert opinion of WG members or the Secretariat.

Synthesis into EtR Framework

- Criterion question: "Is the intervention feasible to implement?"
  The WG/ Secretariat should summarize the evidence, which should include characteristics of the intervention (presentation, formulation, dosage, schedule and flexibility of schedule, special storage requirements) and any barriers to implementation (e.g. barriers related to accessibility, vaccine procurement, licensure, AEFI surveillance, information management). The WG/Secretariat may take into consideration experiences from other countries that introduced the intervention earlier.

Balance of consequences

After the WG/Secretariat has considered all the criteria in the EtR Framework and answered each criteria question based on the documented evidence, they should weigh the consequences of the intervention. Consequences in this sense apply to all of the judgements, evidence and additional information on the criteria questions.

A judgement of the balance of consequences may be made by choosing from six possibilities:

Advantageous consequences **clearly outweigh** disadvantageous consequences in most settings.	
Advantageous consequences **probably outweigh** disadvantageous consequences in most settings.	
The balance between advantageous and disadvantageous consequences is **closely balanced or uncertain.**	
Disadvantageous consequences **probably outweigh** advantageous consequences in most settings.	
Disadvantageous consequences **clearly outweigh** advantageous consequences in most settings.	
There is **insufficient evidence** to determine the balance of consequences.	

If appropriate, the balance of consequences may include the options of the intervention (e.g. if different vaccine schedules, formulations and/or dosages are available and discussed).

Outputs of Step 3

- ✓ A judgement on each of the criterion questions for criteria 1-7.
- ✓ A summary of the evidence supporting the judgement made and any additional information that influenced the judgement for criteria 1-7.
- ✓ A judgement of the balance of all advantageous and disadvantageous consequences.

Step 4

The recommendation

After the WG/Secretariat has determined the balance of the consequences of all the judgements made, the WG/Secretariat should develop a **draft NITAG decision and recommendation** on the policy question. These drafts should then be presented to the NITAG members. The completed EtR Framework showing the logical and evidence-based progression to the recommendation can be used to inform NITAG members on the evidence on which the drafted recommendation is based.

During the NITAG meeting members should discuss the draft decision and recommendation. As a product of the discussion, the whole NITAG should agree on a **final NITAG decision and recommendation.**

A policy brief may be developed to inform the MoH on the NITAG's recommendation and the evidence behind the recommendation.

Synthesis into EtR Framework
Draft NITAG recommendation developed by WG/Secretariat

In the section called "Draft NITAG recommendation developed by WG/Secretariat", the draft NITAG decision, the text of the draft recommendation and additional considerations prepared by the WG/Secretariat should be included. All these elements should be based on the judgements made for each of the criteria questions and relate directly to the judgement on the balance of consequences.

The draft NITAG decision may be selected from the following possibilities:

NITAG recommends the intervention.	○
NITAG recommends the intervention for individuals based on shared clinical decision-making.	○
NITAG does not recommend the intervention (but the comparison, if relevant)	○

If the NITAG discussed different available options of intervention and recommends one specific option or all options, the wording of the provided answers may be adapted (e.g. "The NITAG recommends option x/all options").

The draft recommendation(s) developed by the WG/Secretariat should be indicated in the respective section. Additional considerations the WG/Secretariat would like to present regarding the policy question or recommendation may be indicated in the "Additional NITAG considerations" section, including suggestions for overcoming implementation barriers, proposed monitoring and evaluation needs, and/or areas requiring research to inform future decisions.

Details on evidence gaps should be clearly and transparently communicated in the "Additional NITAG considerations" section, as should advice to the MoH on conducting studies to generate data, if necessary.

Final deliberation and decision by the NITAG

In this section of the EtR Framework the final NITAG recommendation, decision and additional considerations (as needed) are indicated. The section should provide a summary of the NITAG's discussion on the draft recommendation developed by the WG/Secretariat and a brief description of the rationale supporting any NITAG modification of, or disagreement with, the draft recommendation.

Final NITAG decision	
NITAG recommends the intervention.	○
NITAG recommends the intervention for individuals based on shared clinical decision-making.	○
NITAG does not recommend the intervention (but the comparison, if relevant)	○

Policy brief

The completed EtR Framework, though concise, may not have the most appropriate structure to inform the MoH about the NITAG's recommendation and the evidence behind it. Instead, the WG/Secretariat should prepare a policy brief that better serves the needs of the decision-makers. Its purpose is to summarize the evidence and rationale supporting the recommendation. Since the document is targeted at decision-makers in the MoH the format should be clear, consistent and as short as possible (e.g. less than 1500 words). The text should briefly state the policy question and unambiguously convey whether the NITAG recommends or does not recommend the intervention. A sample outline for a policy brief includes the following sections:

- Introduction (including policy question);
- Problem (e.g. disease burden);
- Benefits and harms of the intervention (e.g. vaccine efficacy and effectiveness and risk of serious complications following immunization);
- Balance of benefits versus harms of the intervention;
- Cost-effectiveness of the intervention (if within the NITAG's remit);
- Recommended strategy (specifying intervention (including dosage, schedule, formulation), population (including age groups, sex) and goal of the intervention);
- Implementation aspects.

Once the NITAG has finished deliberations and decided on the recommendation, the policy brief may be drafted drawing from the contents of the EtR Framework. The person within the MoH designated to receive communications from the NITAG should receive the policy brief as soon as possible after deliberations have been completed.

Outputs of Step 4

- ✓ A completed EtR Framework showing the logical and evidence-based progression to the draft NITAG recommendation. This can be used as background material to inform NITAG members
- ✓ A final NITAG decision and recommendation on the respective policy question.
- ✓ A policy brief to inform the MoH on the NITAG's recommendation.

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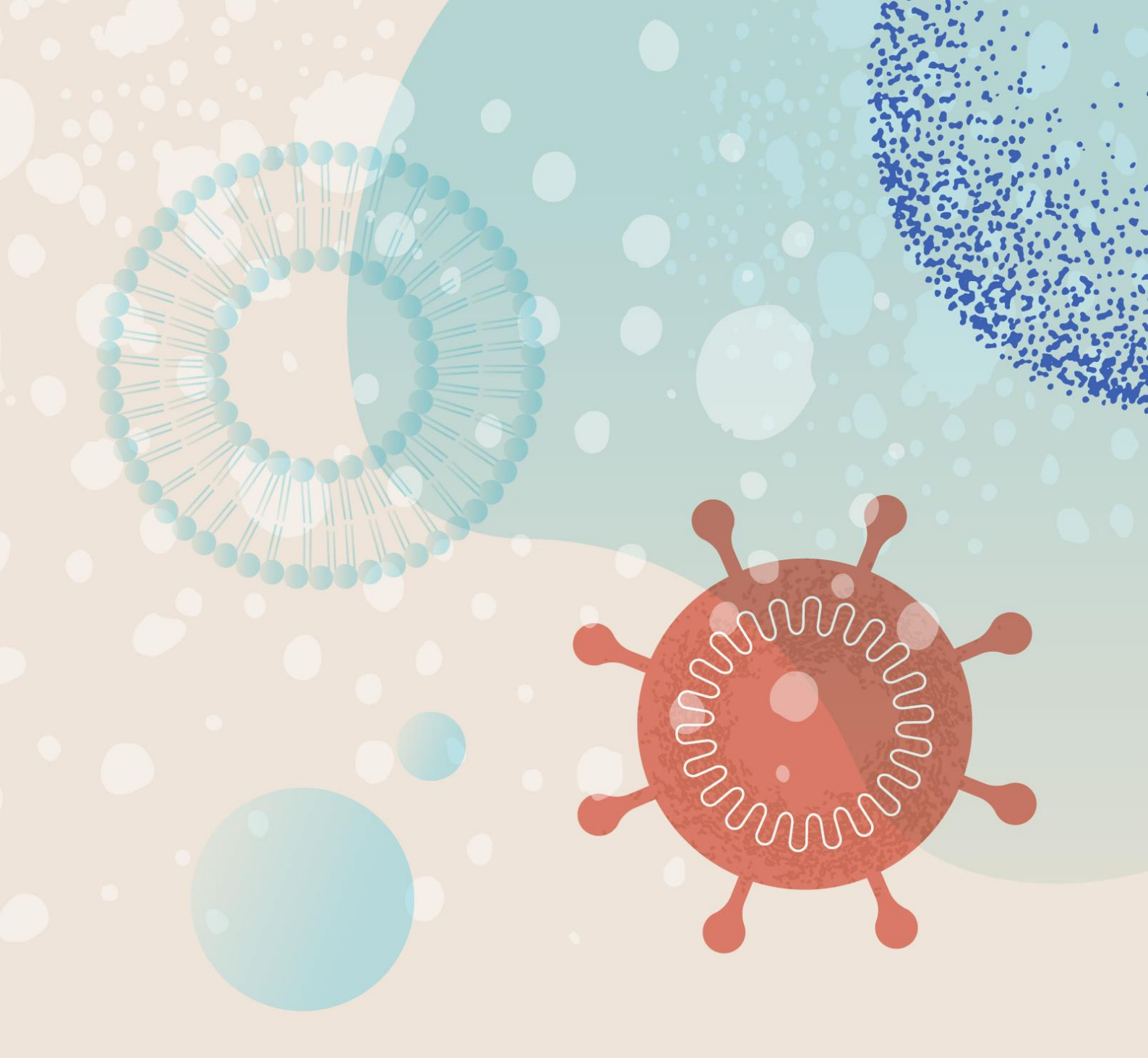
10 Grading of scientific evidence – Efficacy of HPV vaccination in young females. In: WHO position papers on human papillomavirus (HPV) [website]. Geneva: World Health Organization; 2017 (https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/human-papillomavirus-(hpv), accessed 16 March 2022).

11 Grading of scientific evidence – Safety of HPV vaccination in young females. In: WHO position papers on human papillomavirus (HPV) [website]. Geneva: World Health Organization; 2017 (https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/human-papillomavirus-(hpv), accessed 16 March 2022).



APPENDIX 1

Generic Criteria Tables

Criterion 1: **Problem**	
Factors	**Elements**
1.1 Burden/epidemiology of disease	• Frequency of the disease (e.g. incidence, prevalence, secular trends) including in different sociodemographic and age groups • Severity of the disease (e.g. mortality, morbidity) including in different sociodemographic and age groups • Social impact of the disease (e.g. hospitalization rate, school and work sickness absenteeism, effects on high-risk groups and vulnerable populations) • Serogroup or serotype distribution (for serogroup- or serotype-specific vaccines)
1.2 Clinical characteristics of the disease	• Signs and symptoms of disease, severe forms of disease • Long-term complications of disease • Medical management of disease
1.3 Use and costs of health care	• Primary/secondary/tertiary care implications • Short- and long-term use of health care (e.g. treatments, hospitalization)
1.4 Alternative preventive and control measures	• Alternative preventive and control measures (e.g. health education, hygiene) and their effectiveness, costs, and practicality
1.5 Regional and international considerations	• International burden of disease • Disease potential for international spread, and epidemic and pandemic risk

Criterion 2: **Benefits and harms of the intervention** [a]	
Factors	**Elements**
2.1 Efficacy and effectiveness of the intervention (benefit)	• Efficacy and effectiveness estimates (e.g. against infection, disease, hospitalization, death), including in different populations • Immunogenicity, including in different populations • Serogroup or serotype coverage (for serogroup- or serotype-specific vaccines) • Duration of protection and waning of immunity in general and risk groups • Interference with other vaccinees regarding immunity/protection
2.2 Safety of the intervention (harms)	• Type (including severity), consequences and frequency of short- and long-term adverse events following vaccination, including reactogenicity profile • Risk groups or risk factors for adverse events • Contraindications and precautions for vaccination • Potential safety concerns in contacts of vaccine recipients (e.g. for live attenuated vaccines)
2.3 Indirect effects of the intervention	• Herd immunity/protection • Potential impact of strain selection or emergence of non-vaccine serotypes (e.g. serotype replacement)

[a] Interventions comprise vaccine, vaccine dosage, formulation and schedule considered for implementation.

Criterion 3: **Values and preferences of target population** [a]	
Factors	**Elements**
3.1 Perception of target population of the intervention and the disease	• Perception of the target population on the desirable and undesirable effects of the intervention • Perception of the target population on the risk of disease • Acceptability of schedule (e.g. multiple injections, additional visits)
3.2 Differences by sub-groups of target population	• Differences in values and preferences (ethical, religious, financial) for different subgroups of the target population (disadvantaged, religious subgroups)
3.3 Demand	• Demand for vaccination of target population

[a] Addressing not only the population receiving the vaccine, but also their caregivers and/or other groups indirectly affected by the intervention.

Criterion 4: **Acceptability to stakeholders** [a]	
Factors	**Elements**
4.1 Acceptability of the intervention	• Perception of key stakeholders about intervention's advantageous and disadvantageous effects • Acceptability of the vaccine schedule
4.2 Financial, ethical and programmatic considerations	• Ethical, programmatic or financial issues that may affect acceptability of intervention to stakeholders

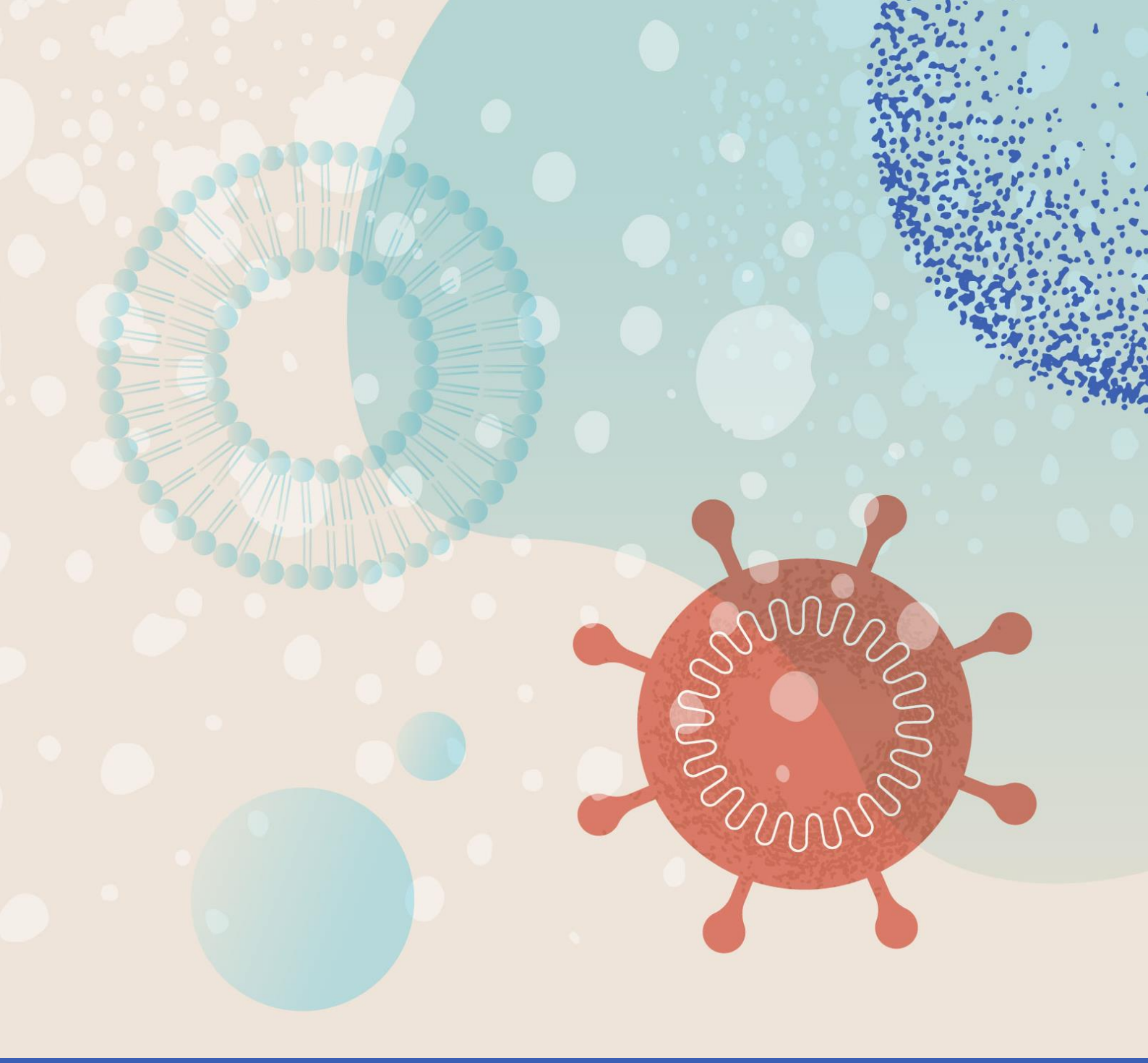
[a] May include the general public, advocacy groups, pharmaceutical companies, professional societies, liaison organizations, and service providers. The groups may differ depending on the vaccines and/or circumstances.

Criterion 5: **Resource use**	
Factors	**Elements**
5.1 Resource use and cost related to the intervention	• Direct cost (e.g. costs of the vaccine, materials, vaccinators, delivery) and indirect costs (e.g. training of health-care workers, supply chain expenses) of administering the intervention
5.2 Socio-economic	• School and work absenteeism • Indirect cost to patients and families • Productivity loss
5.3 Economic impact of intervention on immunization programme and health sector	• Reduction in health-care costs • Cost-effectiveness ratio

Criterion 6: **Equity**	
Factors	**Elements**
6.1 Access to intervention	• Universality, accessibility and gratuity of vaccination services for the entire target population, including vulnerable, hard to reach and immigrant populations
6.2 Ethics, legality of the intervention	• Non-health related effects of intervention, ethical considerations, legal implications
6.3 Stigma	• Stigma around the disease, intervention or alternative preventive or control measures

Criterion 7: **Feasibility**	
Factors	**Elements**
7.1 Vaccine characteristics	• Vaccine presentation, formulation, dosage and route of administration • Administration schedule and possibility of co-administration with other vaccines and drugs • Flexibility of vaccination schedule • Cold chain and logistic requirements
7.2 Accessibility	• Accessibility of vaccination for target population
7.3 Resources for storage, distribution	• Availability of resources for distribution and storage - physical (cold chain storage), human, technical, and financial resources
7.4 Information management	• Availability of information systems to manage the vaccine supply chain and measure related performance metrics (i.e. coverage and vaccine utilization)
7.5 Disease and AEFI surveillance	• Existence and reliability of surveillance systems to monitor disease and AEFI
7.6 Global, regional, local experiences	• Experience from other countries that have introduced the vaccine
7.7 Vaccine availability	• Availability of vaccine and long-term supply • Available suppliers and competition dynamic in the market

AEFI = adverse event following immunization



APPENDIX 2

Evidence to Recommendations Framework

1. Summary of Evidence to Recommendation

1.1 Introduction

Specific policy question: *Overarching policy question to be answered by the NITAG, the specific Working Group (WG) or Secretariat using the Evidence to Recommendations (EtR) Framework. The question should be precisely structured to identify:*

- *Specific intervention (including vaccine schedule, formulation, dosage)*
  *Different options of intervention may be considered (e.g. different vaccine formulations, vaccine dosages, vaccine schedules)**
- *Population targeted for the intervention (e.g. age range, sex, immune status, pregnancy, including specific subpopulations if applicable)*
- *Goal of intervention that should be reached by the introduction in the target group. The goal might be a measurable goal (e.g. reduction of a certain disease) to allow for later evaluation of the impact of the recommendation, but not necessarily.*

If the WG/Secretariat developed a PICO question to facilitate evidence collection on benefits and harms, its components, including comparison and desirable and undesirable outcomes, may be indicated here.

**If different options of the intervention are discussed, incorporate these where applicable into the criteria questions in the "Criteria" section below.*

Background: *The addressed structured policy question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided. If a recommendation is preferential or represents off-label use, this should be indicated. The outcomes indicated in the systematic literature reviews or identified by the WG/Secretariat should be listed.*

1.2 Criteria

Criterion 1: **Problem**		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
Is the problem of public health importance? ○ Yes ○ Probably yes ○ Probably no ○ No ○ Varies ○ Don't know	*Provide available scientific evidence on burden/epidemiology of disease, if relevant within the target population for the recommendation. The use and costs of health care due to the disease, available alternative preventive and control measures, and regional and international considerations may be summarized.* *If evidence is neither available within the country nor from other countries, regions or WHO, provide expert opinion on the public health importance of the problem.*	*Identify any additional public health importance of the problem, including consideration of disparities.* *Indicate any issue regarding the quality of the evidence (transferability, bias, completeness of evidence), if any.*

Criterion 2: **Benefits and harms of the intervention** [a,b]		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
How substantial are the benefits of the intervention? ○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*Describe the magnitude of the benefits of intervention both on the individual (e.g. vaccine efficacy and effectiveness, immunogenicity, duration of protection) and the population level (e.g. herd immunity).*	*Take into consideration:* • *potential differences regarding the benefits across subgroups (by age, gender, pregnancy or lactation status, occupation (i.e. health-care workers), immune status, race, socioeconomic status, and other groups);* • *Other indirect benefits.*
How substantial are the harms of the intervention? ○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*Describe the magnitude of the harms of intervention both on the individual (e.g. adverse events following immunization) and at the population level (e.g. age-shift of disease, serotype replacement).*	*Take into consideration:* • *Potential differences across subgroups regarding the harm. Consider, whether there is a need for a separate recommendation for subgroups based on harms.*

Criterion 2: **Benefits and harms of the intervention [a,b] (cont.)**		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
What is the balance between the benefits and the harms of the intervention? The balance ○ Favours intervention ○ Favours comparison ○ Favours both ○ Favours neither ○ Varies ○ Don't know	*Describe the balance of benefits of the intervention with possible harms. The balance should be described for both the individual and the population level.*	
What is the overall quality of the evidence (meaning here: certainty/ confidence) for the *benefits* (e.g. efficacy/effectiveness, immunogenicity)? ○ high (GRADE level 4, or ⊕⊕⊕⊕) ○ moderate (GRADE level 3, or ⊕⊕⊕) ○ low (GRADE level 2, or ⊕⊕) ○ very low (GRADE level 1, or ⊕) ○ No studies found What is the overall quality of the evidence (here: certainty/ confidence) for the *harms* (e.g. safety, age-shift of disease, changes in serotype distribution)? ○ high (GRADE level 4, or ⊕⊕⊕⊕) ○ moderate (GRADE level 3, or ⊕⊕⊕) ○ low (GRADE level 2, or ⊕⊕) ○ very low (GRADE level 1, or ⊕) ○ No studies found	*If the WG/Secretariat:* • *uses literature reviews conducted by SAGE and/or other NITAGs please refer to the statement on the qulity of evidence provided in the section "Summary of findings" of the GRADE evidence profiles;* • *considered additional elements for the benefits and harms that are addressed by other sources (e.g. other systematic reviews) the quality of the evidence for these elements should be systematically assessed and indicated using a separate line;* • *conducted their own systematic literature review, provide the assessment of the quality of the evidence (e.g. using GRADE)*	*If GRADE was not used the method and/or any other tool used to evaluate the quality of the evidence should be described.*

[a] Interventions comprise vaccine, vaccine dosage, formulation and schedule considered for implementation.
[b] If different options of the intervention are discussed, insert additional rows to answer the questions for each of the options discussed.

Criterion 3: **Values and preferences of target population** [a]		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional Information**
Does the target population feel that the *benefits* of the intervention are large relative to the *harms* of the intervention? ○ Yes ○ Probably yes ○ Probably no ○ No ○ Varies ○ Don't know	*Provide a summary of the evidence on the perspectives and perceptions about the disease and the intervention of the target population, including recipients of the intervention and their caregivers and/or other people indirectly affected by the intervention.*	*If the target population does not value the intervention, or attributes little value to the benefits and harms of the intervention, consider whether potential education measures are needed.*
Is there important uncertainty about or variability in how people value the benefits and harms of the intervention? ○ No important uncertainty or variability ○ Probably no important uncertainty or variability ○ Probably important uncertainty or variability ○ Important uncertainty or variability ○ No known undesirable outcomes ○ Don't know	*Provide available data about important uncertainty regarding how people value the benefits and harms of the intervention. If data suggests important variability in how the target population values the intervention's effects this variability should be indicated.*	*If evidence is limited, WGs'/Secretariats' deliberations can be used.* *If evaluation of people's perspectives, perceptions and preferences is desirable and there is sufficient time, a systematic assessment of how the target population values the intervention may be considered.*

[a] Including not only the population receiving the vaccine but also their caregivers and/or other groups indirectly affected by the intervention.

Criterion 4: **Acceptibility to stakeholders** [a]		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
Is the intervention acceptable to key stakeholders? ○ Yes ○ Probably yes ○ Probably no ○ No ○ Varies ○ Don't know	*Indicate the specific stakeholders considered in the discussion.* *Provide assessment of whether the intervention would be acceptable to these stakeholders (ethically, programmatically, financially etc.). Indicate whether and why acceptability may vary among different stakeholders.*	*The judgement may often represent the expert opinion of the WG/Secretariat.* *Consider the acceptability to stakeholders of alternative prevention and control measures.*

[a] May include the general public, advocacy groups, pharmaceutical companies, professional societies, liaison organizations and service providers. The groups may differ depending on the vaccines and/or circumstances.

Criterion 5: **Resource use**		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
Is the intervention a reasonable and efficient allocation of resources? ○ Yes ○ Probably yes ○ Probably no ○ No ○ Varies ○ Don't know ○ NITAG does not consider resource use to make recommendations	*If data from cost-effectiveness analysis is available (either conducted in the country or from other countries), the findings may be summarized. If several analyses are used the major differences in baseline assumptions should be outlined and the uncertainty of these analyses (if any) and possible variation of the results should be described.*	

Criterion 6: **Equity**		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
What would be the impact of the intervention on health equity? ○ Equity increased ○ Equity probably increased ○ Probably no impact ○ Equity is probably reduced ○ Equity is reduced ○ Varies ○ Don't know	*Summarize the findings addressing issues of health inequities or identified groups who may be disadvantaged by the intervention (or the different options, if any), by the problem or by the alternative preventive and control measures. Include legal and ethical aspects.*	*Consider answering the following questions from the evidence:* • *Are there plausible reasons for anticipating differences in the relative efficacy/effectiveness of the intervention for disadvantaged groups or settings?* • *Are there different baseline conditions across groups or settings that affect the absolute efficacy/effectiveness of the intervention or the importance of the problem for disadvantaged groups or settings?* • *Are there important considerations that should be made when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?*

Criterion 7: **Feasibility**		
Criteria questions and WG/Secretariat judgements	**Summary of evidence**	**Additional information**
Is the intervention feasible to implement? ○ Yes ○ Probably yes ○ Probably no ○ No ○ Varies ○ Don't know	*Summarize the characteristics of the intervention (presentation, formulation, dosage, schedule and flexibility of schedule, special storage requirements).* *Indicate potential barriers for implementation (e.g. barriers to accessibility, vaccine procurement, licensure, AEFI surveillance, information management).*	*Take into consideration experiences from other countries that introduced the vaccine earlier.*

Balance of consequences of intervention

Advantageous consequences **clearly outweigh** disadvantageous consequences in most settings	○
Advantageous consequences **probably outweigh** disadvantageous consequences in most settings	○
The balance between advantageous and disadvantageous consequences is **closely balanced** or **uncertain**	○
Disadvantageous consequences **probably outweigh** advantageous consequences in most settings	○
Disadvantageous consequences **clearly outweigh** advantageous consequences in most settings	○
There is insufficient evidence to determine the balance of consequences	○

1.3 Draft NITAG recommendations developed by WG/Secretariat

Draft NITAG decision (Adapt wording or insert additional lines if different options of the intervention are discussed)	
NITAG recommends the intervention	○
NITAG recommends the intervention for individuals based on shared clinical decision-making	○
NITAG does not recommend the intervention (but the comparison, if relevant)	○

Draft recommendation(s) (text)
Please provide the recommendation(s) proposed to the NITAG.

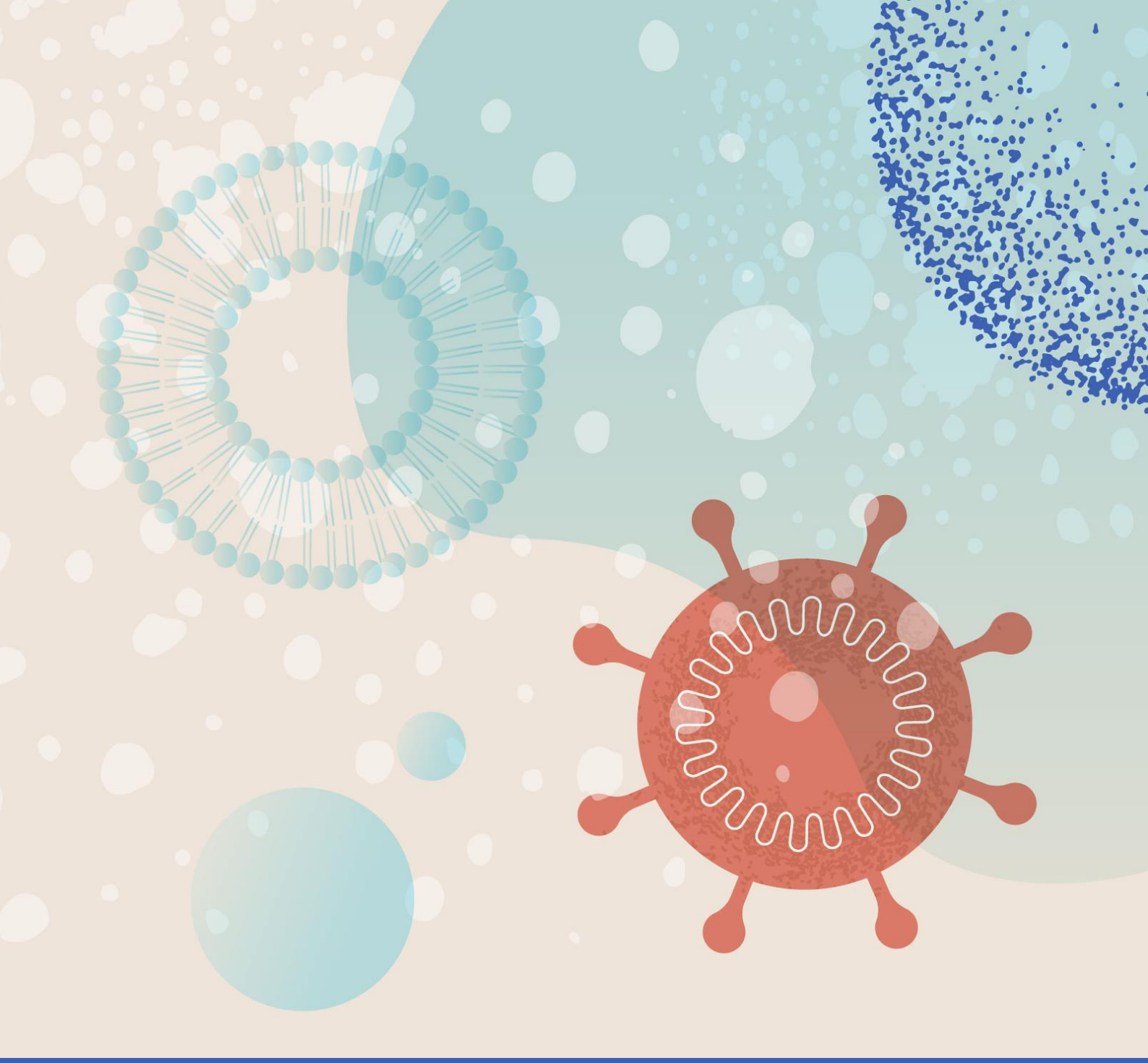
Additional considerations (optional)
Please outline any significant additional considerations (e.g. suggestions for overcoming implementation barriers, proposed monitoring and evaluation needs and/or areas requiring research to inform future decisions).

2. Final deliberation and decision by the NITAG

Final NITAG decision (Adapt wording or insert additional lines if different options of the intervention are recommended)	
NITAG recommends the intervention	○
NITAG recommends the intervention for individuals based on shared clinical decision-making	○
NITAG does not recommend the intervention (but the comparison, if relevant)	○

Final NITAG recommendation(s) (text)

Additional NITAG considerations



APPENDIX 3

PICO question to focus and facilitate a systematic literature review

PICO question to focus and facilitate a systematic literature review

When developing a recommendation on an immunization issue, collection of high-quality evidence on the benefits and harms of an intervention is especially important. A systematic literature review is the best way to collect high-quality evidence. Before embarking on a literature search, a so-called PICO question should be developed to focus the question and facilitate the later literature search. If the question remains undefined, the literature search will also be undefined, leading to an extensive and unfocused result. Please note that the PICO question is different from the policy question developed in the beginning of the EtR Process.

The PICO question predefines the **Population, Intervention, Comparison** and **Outcomes** upon which the later literature search should focus. For each literature review, a separate PICO question needs to be developed. Table A3.1 provides examples from systematic literature reviews conducted on the efficacy and safety of rotavirus vaccination and on the effectiveness and duration of protection of HPV vaccination.

If a literature review is conducted on the efficacy, safety and duration of protection of an intervention, at least three different PICO questions need to be developed, one for each outcome. The population and comparison in the three PICO questions can be the same. However, if a NITAG/WG/Secretariat is interested in the efficacy of a certain intervention in different populations, PICO questions with different definitions of the populations but the same intervention and possibly the same outcomes should be defined.

The **PICO population** is the population (defined according to age group, sex, immune status, geography - as appropriate) which the NITAG/WG/Secretariat considers appropriate/relevant to assess the evidence on benefits and/or harms. The population in a PICO question in which the outcomes are vaccine efficacy and safety usually reflects the population targeted for the intervention, and therefore might be the same as mentioned in the policy question. However, the population in a PICO question in which the outcomes are the duration of protection, the effectiveness or the impact of the intervention usually differs from the targeted population and includes wider age ranges.

The **PICO intervention** is the intervention (e.g. vaccine, vaccine formula, dosage or schedule) on which the NITAG intends to develop a recommendation. For the collected evidence to be transferable, the intervention in the PICO question should be the same as the intervention in the policy question.

The **PICO comparison** defines the other intervention to which the PICO intervention is compared in the studies. For example, studies on the efficacy/effectiveness, safety and/or duration of protection of a new vaccine compare the vaccine to placebo, no vaccination, standard care, other prevention options or another vaccine for an unrelated disease. The comparison should be suitable to assess efficacy, effectiveness, safety and duration of protection.

If the NITAG discusses different available options (e.g. different vaccine formulations, dosages or schedules), the PICO comparison should be the "other option", meaning the other vaccine formulation, dosage or schedule under consideration.

The **PICO outcomes** are all effects of the intervention considered critical or important for recommendation- or decision-making. The outcomes are different from the "Goal of the intervention" included in the policy question, which might be broader than the PICO outcomes. The PICO outcomes may be categorized as desirable (benefits) and undesirable (harms). The desirable outcomes are usually related to the efficacy/effectiveness and duration of protection of the intervention. Immunogenicity can in some instances be a critical/important desirable outcome as well.

The undesirable outcomes (harms) of the intervention relate to an intervention's safety. Both reactogenicity symptoms and adverse events following immunization reported in clinical trials or studies conducted after vaccine introduction may be considered. WHO SAGE identifies undesirable outcomes of interest from safety reviews and/or statements from the Global Advisory Committee on Vaccine Safety (GACVS) and summarizes these in their recommendation.[1] Other indirect undesirable outcomes of the intervention might include replacement of serotypes or shift of the disease to other age groups.

Both desirable and undesirable outcomes can be multiple, but not all may be important for recommendation- and/or decision-making. Therefore, desirable and undesirable outcomes should be ranked as "critical", "important" and of "limited importance". To guide the evidence collection, only the "critical" and "important" outcomes are included into the PICO outcome.

Critical outcomes: desirable and undesirable outcomes that need to be considered and/or that provide information that policy-makers (MoH) would need to make a decision.

Important outcomes: desirable and undesirable outcomes that need to be considered but which would not have as strong an impact on MoH decision-making compared to critical elements.

Outcomes of limited importance: desirable and undesirable outcomes that do not need to be considered.

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[1] Guidance for the development of evidence-based vaccination-related recommendations. Version 8. Geneva: World Health Organization; 2017 (https://www.who.int/publications/m/item/guidance-for-the-development-of-evidence-based-vaccine-related-recommendations, accessed 15 March 2022).

“Critical” or “important” undesirable outcomes do not necessarily or exclusively include serious adverse events. On the contrary, minor clinical factors - such as variations in vaccine reactogenicity or minor local or systemic reactions (e.g. fever, potentially inducing cramps in babies) - may lead to decreased vaccine acceptance among the target group or their caregivers and may therefore be ranked as “important” or “critical”.

Table A3.2 illustrates how a WG/Secretariat addressing a policy question on the HPV and rotavirus vaccines used this prioritization method to rank evidence on desirable and undesirable outcomes.

Table A3.1. Example of PICO

	Rotavirus vaccine	HPV vaccine
Topic of systematic review	Efficacy and safety of rotavirus vaccine (STIKO, 2013)	Effectiveness and duration of protection of HPV vaccination against HPV (STIKO, 2014)
Population	Children < 5 years of age	Girls/women 9-26 years of age, negative for HPV 16 or HPV 18 or before first sexual contact
Intervention	Vaccination with one of the licensed rotavirus vaccines (in this review: Rotarix, RotaTeq)	Vaccination with a licensed HPV vaccine in a schedule 0-1 or 2-6 months (or similar) without booster after completing the vaccination
Comparison	No vaccination	Placebo or no HPV vaccination or any vaccination other than HPV
Outcomes	**Desirable outcomes** Prevention of: • Rotavirus gastroenteritis (RVGE) requiring hospitalization • RVGE, severe • Deaths due to RVGE • RVGE, nosocomial • All-cause diarrhoea, severe • RVGE, any severity **Undesirable outcomes** • Intussusception • Kawasaki disease • Reactogenicity (fever, diarrhoea, vomiting)	**Desirable outcomes** Prevention of: • HPV infection with a high-risk type, incident • HPV infection with a high-risk type, persistent (≥ 6 months) (or similar) • Cervical intraepithelial neoplasia grade 2 or higher (CIN 2+) • Cervical intraepithelial neoplasia grade 3 or higher (CIN 3+)

Table A3.2. Examples of ranked outcomes

Ranked desirable outcomes (benefits) for rotavirus vaccination (STIKO, 2013)	
Ranking	**Specific outcome**
Critical	Prevention of: • RVGE requiring hospitalization • RVGE, severe
Important	Prevention of: • Deaths due to RVGE • RVGE, nosocomial • All-cause diarrhoea, severe • RVGE, any severity

Ranked undesirable outcomes (harms) for rotavirus vaccination (STIKO, 2013)	
Ranking	**Specific outcome**
Critical	• Intussusception
Important	• Kawasaki disease • Reactogenicity (fever, diarrhoea, vomiting)

Ranked desirable outcomes (benefits) for HPV vaccination (STIKO, 2014)	
Ranking	**Specific outcome**
Critical	Prevention of: • Incident HPV infection with a high-risk type • HPV infection with a high-risk type, persistent (≥ 6 months) (or similar) • Cervical intraepithelial neoplasia grade 2 or higher (CIN 2+) • Cervical intraepithelial neoplasia grade 3 or higher (CIN 3+)
Important	-

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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