World Health Organization

Development of WHO immunization policy and strategic guidance

Methods and processes applied by the Strategic Advisory Group of Experts on Immunization (SAGE) to develop evidence-based recommendations

Development of WHO immunization policy and strategic guidance: methods and processes applied by the Strategic Advisory Group of Experts on Immunization (SAGE) to develop evidence-based recommendations

ISBN 978-92-4-009072-9 (electronic version)

ISBN 978-92-4-009073-6 (print version)

Suggested citation Development of WHO immunization policy and strategic guidance: methods and processes applied by the Strategic Advisory Group of Experts on Immunization (SAGE) to develop evidence-based recommendations. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Sales, rights and licensing. To purchase WHO publications, see https://www.who.int/publications/book-orders. To submit requests for commercial use and queries on rights and licensing, see https://www.who.int/copyright.

any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters. All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Contents

This guidance describes the methods and processes of the Strategic Advisory Group of Experts (SAGE) on Immunization in developing evidence-based recommendations, WHO vaccine position papers, and other immunization policy guidance. Its aim is to facilitate the work of SAGE, its working groups and the WHO Secretariat, as well as to inform a wider readership, such as national immunization managers and national immunization technical advisory groups. The document will be updated, as necessary, as the methodology for evidence-based decision-making evolves. Comments and suggestions for improvement are welcome, and should be sent to sageexecsec@who.int.

Abbreviations

ADOLOPMENT	Adoption, adaptation, and de novo development of recommendations
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews (revised version)
DOI	declaration of interest
DSMB	Data and Safety Monitoring Board
EBM	Evidence based medicine
ECBS	Expert Committee on Biological Standardization
EtD	Evidence to Decision framework
EUL	Emergency use listing
FENSA	Framework of Engagement with non-State actors *(WHO)*
GACVS	Global Advisory Committee on Vaccine Safety
Gavi	Gavi, the Vaccine Alliance
GDG	Guideline development group (WHO)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guideline review committee (WHO)
IVIR-AC	Immunization and Vaccines related Implementation Research Advisory Committee (WHO)
LSR	Living systematic review
MI4A	market information for access to vaccines
NITAG	national immunization technical advisory group
NRA	national regulatory authority
NSRI	non-randomized studies of interventions
PHEIC	Public health event of international concern
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QSP	Quality support panel
PQ	Prequalification
RCT	Randomized controlled trial
RITAG	Regional immunization technical advisory group

RoB	Risk of bias
ROBIS	Risk of bias in systematic reviews
ROBINS-I	Risk of bias in non-randomized studies of interventions
SAGE	Strategic Advisory Group of Experts on Immunization
UN	United Nations
WHO	World Health Organization

1 Introduction and scope

Vaccines are one of the most successful public health interventions of all time. Millions of lives have been saved and substantial disability averted due to the advent of critically-needed vaccines. Many resources are devoted to the development and testing of vaccines, leading ultimately to their licensure and use in populations. Nevertheless, market availability of the vaccine products alone does not ensure their appropriate use. The World Health Organization (WHO) plays an important role in providing leadership in global health on vaccine- and immunization-related issues, as well as in shaping vaccine research agendas, providing guidance and standards for the use of vaccines globally in public health, and in supporting country programmes in the optimal use of vaccines.

WHO is committed to providing evidence-based guidance on vaccine use that is based on recent, high-quality data, and assessed by internationally recognized methods, approaches and best practices. Evidence-based public health is defined as the process of systematically finding, appraising, and using contemporaneous research findings as the basis for decisions *(1)*. Evidence-based decision-making in public health emphasizes that decisions should be informed by the best available scientific evidence, as well as other factors such as context, equity, feasibility of implementation, affordability, sustainability, and acceptability to stakeholders *(2, 3)*.

The Immunization Agenda 2030 (IA2030), endorsed by all WHO Member States at the World Health Assembly in 2020, sets an ambitious, overarching global vision and strategy for vaccines and immunization for the decade 2021–2030 *(4)*. IA2030 positions immunization as a key contributor to people's fundamental right to the enjoyment of the highest attainable physical and mental health, and also as an investment in the future, creating a healthier, safer, more prosperous world for all.

Strengthening evidence-based decision-making, with technical input from bodies such as national immunization technical advisory groups (NITAGs) is an important focus area, as set out under the strategic priority 2: "Commitment & Demand" goal: "*Immunization is valued and actively sought by all people, and health authorities commit to ensuring that immunization is available as a key contributor to enjoyment of the highest attainable standard of health as a fundamental right"*. Furthermore, strategic priority 4: "Life-course & Integration" sets the objective to "*strengthen*

immunization policies and service delivery throughout the life-course, including for appropriate catch-up vaccinations and booster doses".

This guidance document aims to help attain these goals by strengthening WHO's normative function. The specific objective is to serve as a reference manual which describes methods, processes and procedures used to issue independent, evidence-based vaccination policy and strategy guidance in line with international standards *(5, 6)*.

The target audience is people involved in developing global and national policy on immunization. It is also intended for any end-user of WHO's immunization guidance, such as national public health officials, managers of immunization programmes and members of NITAGs and regional immunization technical advisory groups (RITAGs). Lastly, it may be of interest to other advisory groups involved with immunization-related aspects, and health professionals and researchers working in the field of vaccine policy and strategy development.

The science underpinning evidence identification and synthesis, and the translation of a body of evidence into recommendations, continuously evolves. WHO is committed to providing guidance that reflects the latest methods, approaches and best practices internationally. This guidance will be regularly reassessed and updated as required.

2 Contributors and roles

2.1 The Strategic Advisory Group of Experts (SAGE) on Immunization

The Strategic Advisory Group of Experts (SAGE) on Immunization is the principal advisory group to WHO on all aspects pertaining to vaccines and immunization. SAGE is charged with advising WHO on overall global policies and strategies for vaccines and other related technologies. It considers the full spectrum of activities covering immunization, from research and development to implementation and delivery, including linkages with other health interventions. The group reports directly to the WHO Director-General. The complete terms of reference for SAGE activities are publicly available *(7)*. As an advisory group, SAGE has no executive or regulatory function. While their mandate is to advise WHO, their policy and strategic advice is currently also used by Gavi, the Vaccine Alliance (Gavi) and the Global Polio Eradication Initiative.

SAGE comprises at least15 renowned international experts in the field of immunization and related disciplines. Members are selected and appointed by WHO following an open call for nominations. Experts come from a broad range of disciplines and professional affiliations, and consideration is given to attaining an adequate distribution of technical expertise, while balancing geographical and gender representation. A list of SAGE members, along with short biographies and an assessment of potential declared interests, is publicly available on the WHO SAGE website *(8)*. SAGE members serve in a personal, individual, and voluntary capacity and, as such, are not representative of any government, agency, or other entity. They have to comply with WHO's rules on declaration of interests. SAGE members receive no remuneration for serving on SAGE.

SAGE supports WHO's normative work on developing recommendations on global immunization policy and strategy, for consideration by WHO Member States, by applying the principles and methodologies of evidence-based public health. When developing evidence-based policy recommendations for a specific intervention, SAGE takes into consideration, in addition to the core benefit–risk assessment, other important contextual elements such as: feasibility and acceptability; epidemiological factors that influence performance of the vaccine, including disease prevalence; the value of the vaccine in the context of other control measures; equity and gender considerations; and cost–effectiveness.

SAGE typically issues recommendations on a class of vaccines for a specific indication. Hence, recommendations apply across products that have the same general characteristics and

performance profile. In rare instances, SAGE handles product-specific matters when only one product is available and/or in the case of a public health emergency of international concern (PHEIC) where rapid policy advice on emerging products is required.

SAGE's advice is presented to the WHO Director-General for approval before being published as WHO's global immunization guidance.

2.2 SAGE working groups

SAGE working groups are time-limited advisory groups established to help SAGE members prepare for an in-depth review on a specific topic area. The list of current and previous SAGE Working Groups for specific health topics can be found on the SAGE working group website *(9)*.

Working groups consist of two SAGE members and 10–12 additional external subject-matter experts who serve in their personal capacities to represent the range of necessary expertise. In the selection of members, consideration is given to achieving an adequate distribution of technical expertise, geographical representation and gender balance.

Members of SAGE working groups are selected and appointed by WHO following an open call for experts. Suitable individuals who expressed interest to past open calls for other advisory groups (such as SAGE) may also be considered. SAGE working group members receive no remuneration for serving on SAGE. A list of working group members, along with short biographies and an assessment of potential declared interests are publicly available on the working group website. Working group members establish close links with SAGE and ensure that the questions presented by SAGE are adequately addressed within the working group proceedings.

On behalf of SAGE, the working group prepares an independent, in-depth evaluation of the scientific and technical evidence via a systematic process (see Methods for the development of WHO policy recommendations) and provides options for policy and strategy development for further consideration by SAGE. The final recommendations are developed by SAGE.

In the course of their proceedings, the working group further highlights knowledge gaps and research questions from the review of evidence, including an assessment of vaccine products under development and need for future products. The development of final recommendations regarding essential further research again lies with SAGE.

2.3 SAGE secretariat

SAGE and its working group is supported by the SAGE secretariat, comprised of WHO staff working within the immunization policy team, which is hosted at WHO headquarters, Geneva, in the Department of Immunization, Vaccines and Biologicals (IVB).

The SAGE secretariat is led by the SAGE Executive Secretary with the support of additional technical, administrative and project management staff.

The immunization policy team is responsible for liaising with RITAGs and supporting NITAGs. RITAGs have been established in each of the six WHO regions; they provide WHO regional directors and countries in the six regions with recommendations on regional immunization priorities and strategies in light of regional epidemiological and social issues. NITAGs are multidisciplinary bodies of national experts that provide evidence-based recommendations to policy-makers and immunization programme managers.

2.4 Steering group on vaccination policy guidance

The steering group on vaccination policy guidance comprises WHO senior staff who have been nominated by the IVB director. It is an internal WHO mechanism which provides critical oversight on the production of WHO vaccine position papers which present WHO's immunization policies and strategic advice. The steering group is not involved in the work of the SAGE working group nor of SAGE: it advises on the need to update vaccine position papers or other vaccination policy guidance documents. Further information on the steering group is provided below (see WHO vaccine position paper development process).

2.5 External contractors

WHO may decide to engage external contractors, with the necessary expertise and without any conflicts of interest, to compile the evidence base that underpin SAGE's recommendations. Contractors may be asked to conduct systematic reviews of literature and appraise the available evidence. Furthermore, WHO may commission mathematical modelling on various aspects, such as the impact or cost–effectiveness of an intervention. All external contractors are required to comply with the WHO Code of Conduct for responsible Research *(10)*.

3 Operations and management

3.1 SAGE work planning

Throughout the year, the SAGE secretariat monitors the global vaccine landscape, tracks data generated by vaccine monitoring and evaluation systems (see Monitoring and evaluation) and informally collects requests for SAGE advice. These requests may stem from within and/or outside of WHO, including from WHO regional offices, technical partners, key stakeholders, SAGE members, the SAGE steering group and the secretariat. The proposed topics are assessed for their suitability for SAGE advice.

On an annual basis, and following consultation with WHO regional offices, potential SAGE topics will be reviewed by the SAGE secretariat, the IVB management, and the SAGE chair. Based on this assessment, the IVB director decides which topics will be considered for SAGE advice within the next 12–24 months, taking into account WHO priorities and resources. These topics constitute the SAGE workplan, which is published on the SAGE website *(11)*.

Some of the aspects considered when establishing the workplan include the following:

- What are the topics requiring the advice of SAGE?
- Is SAGE advice needed or should the topic go to a different advisory body or be grouped into other ongoing work?
- What is the anticipated output or products from SAGE?
- What is the anticipated impact?
- What is the context and the requested time frame for receiving SAGE advice?

Three months prior to each SAGE meeting, the meeting agenda is determined by IVB senior management in consultation with the SAGE secretariat and SAGE chair. The agenda is based on the annual workplan and takes into consideration the required preparatory work and evidence synthesis for SAGE deliberation.

WHO retains the right to add topics to the SAGE agenda at short notice, such as in the context of a health emergency.

3.2 SAGE meetings

SAGE recommendations are issued during SAGE meetings which occur biannually.

Meetings are structured into open and closed sessions. Open, plenary sessions are convened for the purpose of exchanging non-confidential information and views. Attendance is open to SAGE members, the WHO Secretariat, and selected external subject-matter experts, such as e.g. SAGE Working Group members or members from the Immunization and Vaccines Implementation Research Advisory Committee (IVIR-AC), to provide technical input on specific topics.

The specifics of the recommendations are agreed upon in the closed sessions by SAGE members and the WHO Secretariat.

Prior to the SAGE meetings, SAGE members will have received background materials important to the deliberations.

The recommendations are reached by consensus. The quorum is two thirds of members being present during the meeting. If consensus cannot be reached, additional information is sought and the issue is revisited at a later SAGE meeting. If, in exceptional circumstances, consensus on a particular issue cannot be reached, minority opinions will be reflected in the meeting report.

In exceptional situations, such as in the context of a PHEIC, when rapid decisions are required, extraordinary SAGE meetings may be held to issue more immediate advice and guidance to countries.

On rare occasions, SAGE will be asked to issue recommendation outside of plenary or extraordinary SAGE meetings (see Development of rapid advice and emergency response guidance

3.3 WHO endorsement

Following SAGE meetings, whether regular or extraordinary, the SAGE chair presents the WHO Director-General or delegate with a report containing the main meeting outcomes and recommendations. Only thereafter will recommendations be publicly communicated. All recommendations from SAGE are advisory; WHO retains full control over any subsequent decisions or actions regarding proposals, policy issues or other matters considered by SAGE.

Should WHO disagree with the advice given by SAGE, for the purpose of transparency, any divergent view from SAGE will be captured and clearly labelled in the final meeting report.

3.4 SAGE communication

All SAGE-related materials are publicly available on the WHO SAGE website *(7)*. These include the terms of reference for SAGE members, the composition of SAGE and SAGE working groups, meeting materials and reports, and vaccine position papers. Information relating to specific regular and extraordinary SAGE meetings, such as meeting agendas, background documents, presentations, declarations of interest, assessments of SAGE members, and lists of participants are accessible on the WHO SAGE website *(12)*.

In the days following a SAGE meeting, a high-level summary of the deliberations is released in conjunction with a press event. A comprehensive meeting report is published in the WHO Weekly Epidemiological Record approximately six weeks after the meeting *(13)*.

WHO's official advice on matters that result in a vaccination policy or an update to an existing policy is reflected in the WHO vaccine position papers published approximately three months after the respective meeting in the WHO Weekly Epidemiological Record (see Development, publication and update of WHO vaccine position papers and other policy guidance).

Interim or emergency guidance (see Development of rapid advice and emergency response guidance are published in an accelerated process after the meeting on the WHO SAGE website.

3.5 Declaration and management of interests

The work of WHO and the contributions of its experts must be – and must be perceived to be – objective and independent. In this regard, and to ensure the highest integrity and public confidence in its activities, WHO requires experts who serve in an advisory role to disclose any circumstances that could give rise to a potential or reasonably perceived conflict of interest related to the subject of the activity in which they will be involved *(14)*.

"Conflict of interest" is defined as any potential interest declared by an expert serving in an advisory role, either financial or intellectual, that may affect or reasonably be perceived to affect the individual's objectivity and independence in providing advice to WHO, and/or create an unfair competitive advantage for the individual, or for persons or institutions with whom the individual

has financial, business or other interests (such as adult children or siblings, close professional colleagues, administrative unit or department).

A conflict of interest analysis is performed prior to the nomination of any new SAGE member and before each SAGE meeting. For this, a WHO declaration of interest form for vaccine- and immunization-related interests must be completed and submitted to the SAGE secretariat (Annex 1).

The SAGE secretariat, with the assistance, when required, of the WHO Office of Compliance, Risk Management and Ethics, thoroughly assesses and judges all declared interests on a case-by-case basis. Final decisions are made by WHO on the same basis.

All relevant interests that have arisen during a period of 4 years preceding the appointment for SAGE membership, or the specific SAGE meeting, will be individually assessed, and the nature and value of the interest, i.e. intellectual property (e.g. patents), and financial and/or investments, considered. The relevance and specificity of the declared interest, in view of the subject matter of the SAGE meeting or work to be undertaken, is evaluated, as well as the timeliness of the interest.

A declared interest is considered insignificant or minimal if it is unlikely to affect, or be reasonably perceived to affect, the judgement of the SAGE member. Insignificant or minimal interests generally are unrelated or only tangentially related to the subject of the activity or work and the outcome; nominal in amount or inconsequential in importance; or expired (>4 years ago).

There are three possible implications of a reported interest from a SAGE member:

1. The SAGE member can take part in full in all of the discussions during the SAGE meeting.

2. The SAGE member will only be allowed to take part in the discussion but not in the recommendation-making.

3. The SAGE member will be excluded from both the discussion and recommendation-making of that portion of the work where the conflict of interest has been identified.

A public disclosure of the summarized reported interests of SAGE members and the possible implications for engagement will be posted on the WHO SAGE website, for public comment, 4

weeks prior to each SAGE meeting. The final summary of declared interests is posted on the WHO SAGE meeting website.

The procedure for reporting and assessing conflicts of interest applies equally to experts serving on SAGE working groups. Potential conflicts of interests are summarized and made publicly available on the SAGE working group website *(15)*.

In addition, WHO staff working within the SAGE secretariat and on the steering group are required to provide an updated declaration of interests form annually, which is revised and managed by the WHO Office of Compliance, Risk Management and Ethics.

Any expert serving on SAGE or its working groups will be required to sign the standard WHO Confidentiality Undertaking.

3.6 Funding

The structures and principles guiding resource acquisition and allocation to WHO policy development processes are designed to safeguard the independence of parties involved, as well as to ensure that funders do not influence content or recommendations.

Funding to WHO can be categorized into distinct groups *(16)*:

- Assessed contributions (country membership dues): these are calculated relative to a country's wealth and population and approved every two years by WHO Member States at the World Health Assembly. As highlighted earlier, SAGE members receive no renumeration for their contributions to the work of SAGE.
- Voluntary contributions: these come largely from Member States, as well as from other United Nations organizations, intergovernmental organizations, philanthropic foundations, the private sector, and other sources.

Activities of the SAGE secretariat, SAGE and SAGE working groups may be funded through assessed or voluntary contributions. Voluntary contributions may be accepted following careful evaluation, compliant with WHO's Framework of Engagement with non-State actors (FENSA) *(17)*.

4 Methods for the development of WHO policy recommendations

This section summarizes the processes and methods for developing WHO's vaccine and immunization-related recommendations. The processes and methods related to the development of WHO normative guidance can be found in the WHO handbook for guideline development *(6)* or in Evidence, policy, impact: WHO guide for evidence-informed decision-making *(5)*.

4.1 Policy and PICO questions

The policy questions to be answered by SAGE and its working groups on behalf of WHO are often broad and overarching. For example, the policy question may ask whether a certain vaccine should be introduced through a routine vaccination programme.

Structuring the broad policy question into specific elements that guide the collection and assessment of evidence is a well-recognized step in evidence-based medicine. The appropriate translation of a policy question into a research question should be performed at the initial stage of the working group proceedings to allow sufficient time for review of the evidence.

Systematic reviews of literature, which attempt to identify all related publications on a given topic, are the chosen method to support evidence-based practices and health-care decisions through a quantitative or qualitative approach which assimilates the identified literature with the help of statistical analysis.

A critical factor in obtaining an unbiased systematic review is a comprehensive and structured search process, conducted independently with clearly-formulated research questions.

The PICO (population, intervention, comparison and outcome) model was developed in 1995 *(18)* and is now commonly used to ensure that research questions are framed effectively for the quantitative systematic review of literature. All research questions must be focused and well-articulated.

The PICO framework focuses on population, intervention (or exposure), comparison and outcomes to identify different components of evidence for a systematic review *(19)*:

Population

The definition of "population" should be specific and narrow. For example, in the context of human papillomavirus (HPV) vaccine, the focus may be on girls aged 9–14 years, whereas for

rotavirus vaccine, the population would encompass infants under 6 months of age. Therefore, it may be useful to specify the context (for example, girls aged 9–14 years in low- and middle-income countries).

Intervention

Interventions may range from the introduction of a new vaccine or a new vaccine formulation, to a new vaccination schedule, such as hexavalent diphtheria, tetanus, pertussis, haemophilus influenzae type B, poliovirus and hepatitis B (DTaP-Hib-IPV-HepB) combination vaccines; 1-dose HPV vaccine; and hepatitis B birth-dose vaccine.

Comparator

The most appropriate comparator may be no vaccination, placebo, variations of the to-date schedule, or an alternative competing vaccine. For example, as a comparator to vaccination with a single-dose HPV vaccine scheme, using a 2-dose vaccination schedule or no vaccination may be considered.

Both intervention and comparator should be defined in detail, including mode of administration, dosage, schedule or duration.

Outcome(s)

Outcomes should be judged as those most important for policy-making and may include disease endpoints (e.g. death, severe disease or hospitalization). At times surrogate outcomes may be considered (e.g. immunogenicity in the case of an established correlate of protection).

Outcomes that are critical for decision-making should be considered. Furthermore, it is necessary to differentiate between outcomes that are important but not critical, and those that are not important. GRADE *(19)* specifies three categories of outcomes according to their importance for decision-making:

1) critical
2) important but not critical
3) of limited importance.

To facilitate ranking according to importance, outcomes may be rated numerically on a scale of 1–9 (7–9 = critical; 4–6 = important; 1–3 = of limited importance). Only outcomes considered critical (i.e. rated 7–9) influence a recommendation or are used to determine the overall certainty of evidence supporting a recommendation.

Of note is that, at times, the importance of a specific outcome (e.g. a serious adverse effect) may become known only after the protocol has been written, the evidence reviewed, or the analyses carried out. Therefore, the working group may adjust the ranking of outcomes after first sighting of the literature review.

In general, and particularly for new vaccines, three outcomes need to be considered within the systematic review of literature: i) vaccine efficacy/effectiveness/immunogenicity; ii) vaccine safety; and iii) duration of protection.

The framing of questions relating to vaccine safety is of particular importance and should focus on the potential occurrence of serious and specific adverse events. However, other factors, such as variations in vaccine reactogenicity and more minor local or systemic reactions (e.g. fever), must also be considered when making recommendations. Evidence of causality between vaccination and adverse events must be sought.

The PICO format may not be applicable for other key questions, such as those on disease burden, economic considerations or strategic recommendations (e.g. research gaps, decisions to pursue an eradication goal, etc.). In these instances, appropriate tools, such as mathematical modelling and cost–effectiveness evaluations will be identified to address these questions.

4.2 Types of evidence, retrieval and synthesis

In line with internally recognized standards, randomized-controlled trials (RCTs) are considered the gold standard for any vaccine-related assessment. However, additional types of evidence to support decision-making may be used. These evidence types include:

- observational data, mainly from vaccine effectiveness and safety studies, including from outbreak investigations, post-market disease or vaccine surveillance studies;
- programme evaluations;
- disease or vaccination impact modelling;
- cost–effectiveness evaluations;

- global market dynamics and supply estimates; and
- other types of data, such as qualitative evidence, that may be relevant and are considered necessary by SAGE.

All of the above-mentioned types of evidence represent important information sources and constitute the most significant part of the body of evidence used as the basis for SAGE recommendations. The collation and assessment of certainty is explained in the section on Risk-of-bias assessment.

4.2.1 Peer-reviewed publications

Data that have been collected, assessed systematically, and published in high-quality, peer-reviewed journals, should serve as the basis for any policy or strategic advice.

4.2.2 Preprints

The use of preprints as a basis for policy should be avoided, the aim being to rely on evidence published in peer-reviewed scientific journals. However, in exceptional circumstances such as the COVID-19 pandemic, preprints have proven an important source of information where rapid access to emerging data was paramount. The need for timely advice must be balanced against the risk of introducing bias based on preliminary, non-peer-reviewed data. Any interim recommendation based on data from preprints will be revisited when more solid evidence becomes available (see Development of rapid advice and emergency response guidance

4.2.3 Unpublished data

All evidence that underpins SAGE recommendations must be made publicly available. Sometimes, to ensure the timely publication of recommendations, revised data will be used that are not yet in the public domain. Such situations may include vaccine manufacturers providing unpublished data to WHO, for example in the context of regulatory assessment documents. With any unpublished data, it is essential that sufficient information on the methodology is provided, so that confidence in the certainty of evidence can be meaningfully assessed. Should no public source of information (e.g. peer-reviewed publications, preprints) be available when related recommendations are issued, WHO requires the data to be published as part of the publicly available background documents developed in preparation of a SAGE meeting. Such data must be properly referenced (e.g. as “in press” publications or by reference to the host web address). SAGE will not issue a recommendation if the related data are not publicly available.

Sources of evidence may include both primary (published or unpublished) and secondary data. Concerted efforts should be made to identify any unpublished but relevant data that would inform SAGE deliberations, granted the permission to make accessible the retrieved evidence.

4.2.4 Systematic reviews

A detailed methodological overview of systematic literature reviews can be found in the Cochrane handbook for systematic reviews of interventions *(20)* or in Developing NICE guidelines: the manual *(21)*. Carrying out a literature search that is carefully documented, transparent and reproducible involves five phases. First, a review protocol is developed which specifies the objective of the review; PICO questions; study inclusion and exclusion criteria; search strategy; data collection; quality assessment; and data synthesis. Next, a systematic literature search is conducted, which involves identification of information sources, development of a search strategy, management of references, and documentation of the search procedure. Following this, the study selection step identifies search results that meet the specified inclusion criteria; data on study characteristics and outcomes from included studies are then extracted using a standardized data extraction tool. Finally, if appropriate, data may be synthesized by meta-analysis (for quantitative studies) or other approaches (for qualitative or mixed-method studies).

A comprehensive systematic literature review is generally carried out by a commissioned independent third party. At times, reviews are conducted by members of the working groups or by WHO.

When available, a recent, relevant, high-quality systematic review can be used as a basis for SAGE policy in lieu of commissioning a de-novo systematic review. The SYSVAC 2[1] project was launched to guide policy-makers to vaccine-related systematic reviews and assist with their quality appraisal (see Resources) *(22, 23)*. If a high-quality but dated systematic review is available, it can be updated to reflect new publications.

Completed systematic literature reviews, including those that are pre-existing, are assessed to ensure their completeness. Data should be extracted and consolidated using a data extraction tool and a list of relevant papers (including access to the full content of the manuscripts).

[1] SYSVAC (Systematic Reviews on Vaccines) is a global registry set up by The Robert Koch Institute and collaborators to facilitate the retrieval of systematic reviews to strengthen national immunization programmes and decision-making processes.

SAGE may request the WHO Global Advisory Committee on Vaccine Safety to conduct post-introduction safety assessments *(24)*.

4.2.5 Rapid reviews

Depending on scope, the time taken to conduct systematic reviews may range from several months to up to a year. In situations where timely advice is needed (e.g. in the context of a PHEIC), commissioning a new systematic review may not be feasible or a good use of the available resources. While there is no standard definition of rapid reviews, they share in the simplification or omission of components of a systematic review with the purpose of expediting decision-making *(25)*. Preliminary guidance has been developed to support the conduct of rapid reviews while ensuring minimum standards *(26)*.

4.2.6 Living reviews

"Living systematic review" is an approach that aims to continually update a review, incorporating relevant new evidence as it becomes available. Living systematic reviews have proven particularly important in fields where research evidence is emerging rapidly, current evidence is uncertain, and new research may change policy or practice decisions *(27)*.

A living systematic review and living evidence synthesis were used in the context of COVID-19 vaccination, where SAGE was asked to provide timely advice on emerging vaccines *(28)*.

4.2.7 Mathematical modelling

Modelled evidence often informs important strategic or policy questions. Hence, mathematical models are used as part of the evidence in support of SAGE recommendations. In order to assure the quality of these models, WHO's Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) may be solicited *(29)*.

IVIR-AC is a standing advisory committee and principal advisory group to WHO. The committee provides independent appraisal of, and advice on, implementation research related to vaccines and immunization to inform public health decisions, including issues raised in discussions by SAGE.

IVIR-AC organizes biannual meetings that precede SAGE meetings. Ad-hoc reviews between the biannual meetings can be called upon to support urgent policy guidance by SAGE or other bodies. Ad-hoc reviews may not need the involvement of the full committee; they can be led by the SAGE chair with two additional members, complemented, if necessary, by subject-matter experts.

IVIR-AC reviews and clarifies the questions posed for mathematical modelling by assessing the nature and appropriateness of the modelling methods; by contributing to assessing the underlying assumptions as well as the data and model parameters used; and by reviewing the applied use and interpretation of the modelling outputs for decisions.

To inform important policy questions from SAGE, IVIR-AC encourages the use of multiple-model comparisons, rather than relying on modelled evidence from one group only. The reason for this is to: a) increase understanding and transparency of modelling methods; b) characterize the robustness of different model predictions to changes in inputs, structures, assumptions and parameters, to assess their impact for policy recommendations; and/or c) to synthesize conclusions from several models in order to inform policy recommendations *(30)*. IVIR-AC further assists SAGE with implementation research questions including reviewing and advising on quantitative methods in vaccine research.

While IVIR-AC may review a finished model and its outputs, a more effective and efficient use of the committee is to obtain a consultation before the modelling has begun and when the policy questions are first identified. If needed, the SAGE secretariat and the IVIR-AC secretariat can jointly establish a SAGE working group – i.e. a subgroup on impact modelling, to translate policy questions into modelling questions; issue requests for proposals; identify models that are appropriate to address the questions; commission modelling work; and review assumptions, inputs, and outputs from the work.

4.2.8 Vaccine market data

The WHO initiative, Market Information for Access to Vaccines (MI4A) *(31)*, was launched in 2018 to contribute to the achievement of Sustainable Development Goal 3.8 (a Universal Health Coverage target) by enhancing access to safe, effective, high quality, and affordable vaccines for all. MI4A is part of the broader WHO effort to ensure availability of essential medicines and responds to specific requests from WHO Member States and SAGE to address gaps in vaccine market information. The MI4A assessments and global market studies were established to understand the dynamics of global vaccine demand, supply and pricing; and to identify affordability and shortage risks. As SAGE aims to account for these systematically in its recommendations when required, such studies are becoming increasingly important.

4.3 Risk-of-bias assessment

Studies identified in the systematic literature review should be documented in a summary table and associated with a methodological evaluation of the risk of bias of the included literature. This process allows for the easier comparison and evaluation of studies when scoring the quality of scientific evidence.

Several factors may put studies at a higher risk of bias (i.e. systematic error) and these need to be considered when determining the quality of the evidence. Multiple tools are available for evaluating study quality: for SAGE, the use of established, widely-used tools, such as the ones presented below, is preferred.

4.3.1 Risk-of-bias appraisal of randomized controlled trials

When properly conducted and of adequate size, RCT study designs have the lowest risk for bias. The revised Cochrane collaboration Risk-of-Bias 2 (RoB 2) tool for randomized trials *(32)* provides a framework for assessing the risk of bias in the findings of any type of randomized trial. The tool is structured into five domains through which bias can be introduced into the result. The five domains concerning the risk of bias in RCTs that require consideration are:

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result.

Signalling questions act as an algorithm to make a judgement in each domain. Possible outcomes for each domain are high risk, some concerns, or low risk, generating an overall judgement. Each feature should be evaluated to determine the risk of bias in each study (using the data extraction tool and checklist) and then documented in the summary table for evidence review. Adaptations exist for cluster and cross-over RCTs; details are provided in the related guidance document *(33)*. In addition, learnings and recommendations for users of the RoB 2 tool, following its implementation, can be found in a Cochrane guidance *(34)*.

4.3.2 Risk-of-bias appraisal of observational studies

Observational studies are particularly susceptible to selection bias and confounding. As different types of observational studies carry different risks of bias, it is more challenging to standardize the evaluation of bias across study types.

The Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool has been developed to assess risk of bias in the results of non-randomized studies of interventions (NRSIs) that compare health effects of two or more interventions *(35)*.

The types of NRSI that can be evaluated using the ROBINS-I tool are quantitative studies estimating the effectiveness (harm or benefit) of an intervention, which did not use randomization to allocate participants to comparison groups. This includes studies where allocation occurs during the course of usual treatment decisions or peoples' choices. These are often called "observational" studies and include cohort studies, case–control studies, controlled before-and-after studies, interrupted-time-series studies and controlled trials in which intervention groups are allocated using a method that falls short of full randomization (sometimes called "quasi-randomized" studies) *(36)*.

The ROBINS-I tool covers seven domains through which bias may be introduced into an NRSI. The first two domains address issues before the start of the interventions that are to be compared ("baseline"); the third domain addresses classification of the interventions themselves. The other four domains address issues after the start of interventions.

Responses to signalling questions for the RoB 2 tool provide the basis for domain-level judgements about risk of bias. Possible outcomes for the risk of bias per domain are low risk, moderate risk, serious risk, critical risk and no information; these are also the categories for the overall risk of bias judgement. Further details can be found in the related guidance document *(37)*.

4.3.3 Risk-of-bias appraisal of systematic reviews and meta-analysis

Systematic reviews and meta-analyses can be useful tools for evaluating effects across studies. Their validity depends on the completeness of the literature search; the thorough assessment of study quality; the appropriateness of combining data across studies; and the relevance of the outcomes considered. In assessing the quality of an existing systematic review, careful attention should be paid to the search methodology, heterogeneity, and inclusion/exclusion criteria

(particularly for observational studies), in addition to the quality of the design and methodology of individual studies. If any of these are in question, the results of the systematic review should be viewed cautiously. Some reviews do not consider all of the data that may be relevant to an assessment of vaccine efficacy and safety (e.g. observational studies, outbreak investigations, surveillance reports, etc.). Key appraisal tools for systematic reviews and meta-analysis that include randomized or non-randomized studies of health-care interventions, or both, include the Risk of Bias in Systematic Reviews (ROBIS) tool *(38)* as well as the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) tool *(39)*.

ROBIS

ROBIS is completed in three phases: Phase 1: assess relevance (optional); Phase 2: identify concerns with the review process; and Phase 3: judge risk of bias. Phase 2 covers four domains through which bias may be introduced into a systematic review:

- Study eligibility criteria
- Identification and selection of studies
- Data collection and study appraisal
- Synthesis and findings

Signalling questions are included to help judge concerns with the review process (Phase 2) and the overall risk of bias in the review (Phase 3).

AMSTAR 2

The revised instrument (AMSTAR 2) retains 16 domains; seven of these are considered critical:

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15).

The overall rating of the confidence in the results of the review can be grouped into high, moderate, low and critically low.

4.4 Rating the certainty of the evidence using GRADE

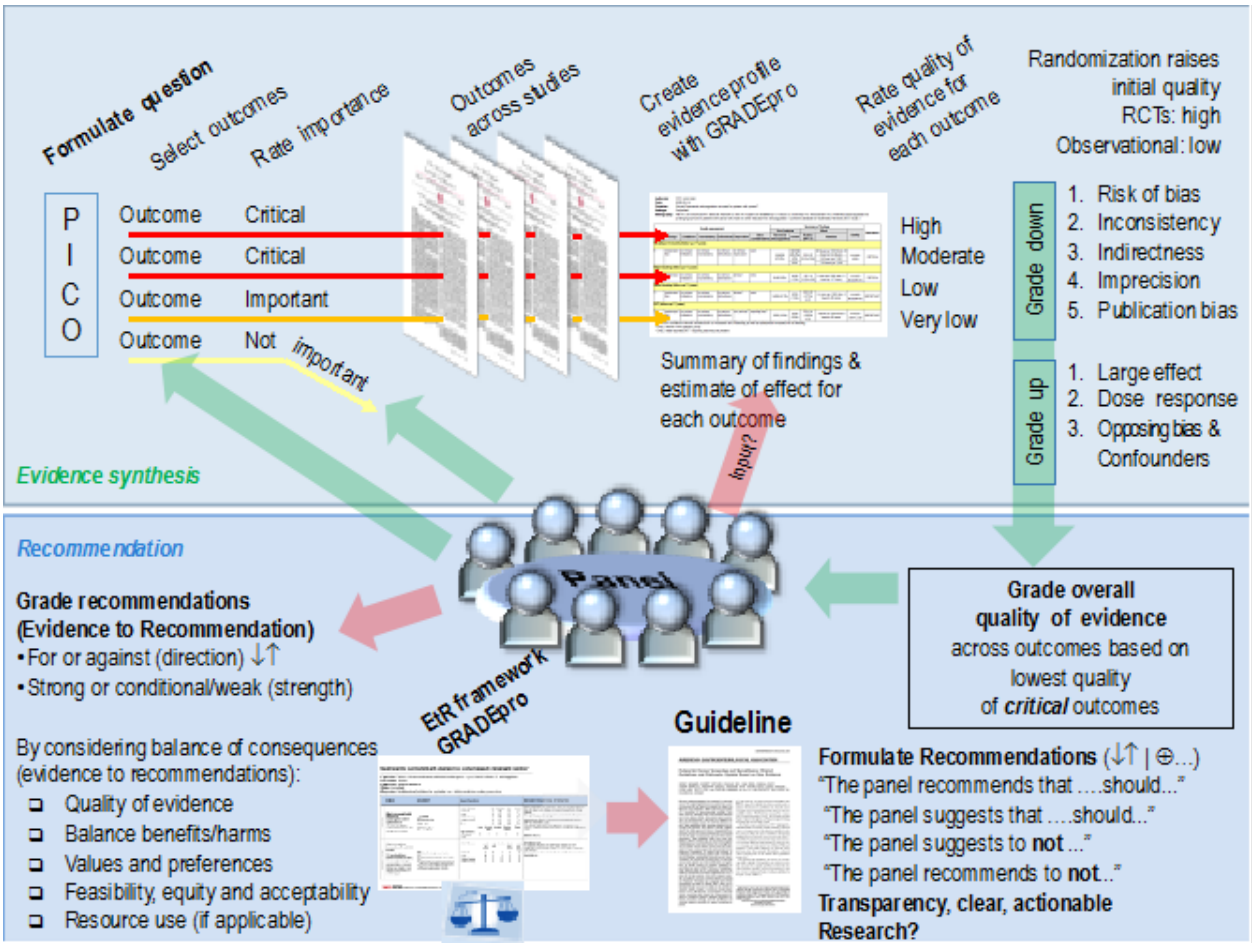
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) *(40)* approach to evaluate evidence is the most prominent of the many frameworks developed over the years to assess the certainty (or the quality) of a body of evidence in order to determine whether the effect estimates are adequate to support a recommendation.

In the context of evidence syntheses, GRADE defines the certainty of evidence as the "extent to which one can be confident that an estimate of the effect or association is correct" *(41).* GRADE has been adopted by WHO and many other national and international organizations. The use of the GRADE methodology as an approach to rate the certainty of evidence in support of key recommendations included in the WHO vaccine position papers began in April 2007.

GRADE provides a framework for assessing quality that encourages transparency and an explicit accounting of the judgements made. Documenting the process of quality assessment in an open way allows others to review the process and contextualize recommendations.

Evidence underlying the critical recommendations is rated using the GRADE framework with formal scoring to assess the quality of related evidence. GRADE distinguishes between quality assessment conducted as part of a systematic review and that undertaken as part of guideline development. Information about study limitations, imprecision, inconsistency, indirectness, and publication bias is necessary for decision-makers to understand and have confidence in the assessment of certainty of evidence and estimate of effect size. The GRADE approach results in an assessment of the certainty of a body of evidence as high, moderate, low, or very low. GRADE's approach to rating the quality of evidence begins with the study design (trials or observational studies), then addresses five reasons to possibly rate down the quality of evidence, and three to possibly rate up the certainty *(41).* Based on this, the panel (SAGE) formulates recommendations based on the quality of the evidence (alongside other important criteria (see Evidence-to-decision tables) (Figure 1).

Figure 1. GRADE processes to evaluate evidence, present summary findings, and create evidence-based recommendations*



*Adapted from the GRADE handbook (https://gdt.gradepro.org/app/handbook/handbook.html), and based on the GRADE meeting, Edinburgh 2009.

Assessment of GRADE certainty of evidence

Only primary data sources should be entered into GRADE tables. Both published and unpublished studies may be included provided that they are in press, a preprint or otherwise publicly accessible. Studies enter into the GRADE system at an initial level based on their study design. Initially, all RCTs enter at level 4 – i.e. the highest level of certainty of evidence; non-randomized studies generally enter at level 2 – i.e. a low level of certainty of evidence. Nevertheless, the use of ROBINS-I in GRADE assessments allows for a better comparison of evidence from RCTs and non-randomized studies because they are placed on a common metric for risk of bias *(42).* Therefore, the certainty of evidence from non-randomized trials could be judged as high in the initial GRADE assessment.

Table 1 and Table 2 outline the criteria for downgrading and upgrading the strength of evidence after its initial entry into the framework. Each downgrading or upgrading of evidence needs to be succinctly footnoted and justified in the GRADE summary table. The brief associated descriptions provide specific instructions on how to apply GRADE to the area of vaccines and vaccination. More detailed information may also be found in the GRADE-publication series in the Journal of Clinical Epidemiology *(43)*.

Table 1. Criteria used to downgrade the certainty level of evidence*

Limitations: Quality rating may be downgraded by 1 or 2 levels for serious or very serious methodological limitations in the studies. Examples of these limitations include: inappropriate randomization; lack of concealment; violation of the intention to treat principle; inadequate blinding; substantial loss to follow-up; and early stopping for benefit.
Inconsistency: Quality rating may be downgraded by 1 or 2 levels if the effect is not similar and heterogeneous across studies, and if inconsistencies are serious or very serious.
Indirectness: Quality rating may be downgraded by 1 or 2 levels if there are serious or very serious issues with indirectness. Examples of indirectness may include: use of surrogate endpoints; use of immunogenicity versus clinical endpoints; indirect comparisons between two treatments; potential problems with generalizability to the population of interest; and test inaccuracies. It is suggested that when assessing clinical protection, there is no downgrading for immunogenicity studies when there are well-established standard correlates of protection.
Imprecision: Quality ratings may be downgraded by 1 or 2 levels if there is serious or very serious imprecision (i.e. confidence intervals are wide or very wide). Where possible, imprecision should be assessed using 95% confidence intervals of pooled relative risks (RRs) or odds ratios (ORs) (using meta-analysis techniques), as opposed to looking at 95% confidence intervals of individual studies.
Reporting bias: Quality ratings may be downgraded by 1 or 2 levels if publication bias (i.e. failure to report studies), and selective outcome reporting bias (i.e. failure to report outcomes) are likely or very likely.

*****Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64:1311–6 *(44)*.

Table 2. Criteria used to upgrade the certainty level of evidence*

Large effect/strength of association: Quality rating may be upgraded by 1 level if there is evidence from randomized controlled trials (RCTs) or observational (including surveillance) studies of vaccine effectiveness of 50% or higher (OR/RR ≥2 or ≤0.5[a]) *(44)* with no major[b] residual confounders.

Quality rating may be upgraded by 2 levels if there is strong evidence from RCTs or observational studies of a vaccine effectiveness of 80% or higher (or depending on the outcome, OR/RR ≥5 or ≤0.2) with no major residual confounders. If RCTs suffer very serious methodological limitations, then upgrading for large effect should not be applied.

Population effect (dose–response gradient at population level): Quality rating may be upgraded if there is evidence of a dose–response gradient at the population level, i.e:

- Increase by 1 level if there is evidence of some risk reduction in disease incidence with increasing population vaccine coverage. Evidence of decreased risk with increased vaccine coverage includes evidence of reversal at population level (in situations where programme failure leads to a decrease in vaccine coverage, and subsequent disease return), and evidence of risk reduction in older or younger age groups not targeted for the intervention, but who benefit from herd immunity.
- Increase by 2 levels if there is evidence of high population risk reduction with increasing population vaccine coverage in many different settings based on strong evidence of many years, and/or evidence of reversal at population level (in situations where programme failure results in a decrease in vaccine coverage followed by a return of disease.[c])

Mitigated bias and confounding

Major confounders:[d] Quality rating may be upgraded by 1 level if all major confounders have reduced the demonstrated effect (or increased the effect if no effect was observed).

Or

Good quality study design: Quality rating may be upgraded by 1 level if there was a good quality of study(ies) design to control for confounding and selection biases among cases and controls e.g. with population-based record linkage, self-controlled case series or other appropriate designs.

The quality rating may be further upgraded by 1 level if there is consistency between studies across different settings, different investigators and different designs.[e]

***** Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64:1311–6 *(44)*.

[a] These thresholds refer to risk ratios. When baseline risk is low (i.e. below 20%), odds ratios and risk ratios are very similar and applying these criteria is feasible. When the baseline risk is high (a rare occurrence for vaccine preventable diseases) and the effect size is large, odds ratios can be far larger in magnitude than risk ratios. Under such circumstances, a higher threshold for odds ratios may be appropriate.

[b] Changed from "plausible" confounders in the formal GRADE framework.

[c] This increase by 2 levels is not directly reflected in the current GRADE rating scheme and collaboration with the GRADE working group will continue to further optimize the process. The GRADE working group, however, recognizes that in some circumstances other considerations may lead to upgrading as appropriate. This is an example of other criteria that have been determined by SAGE to be applicable for upgrading.

[d] This criterion has been slightly modified from the GRADE criteria, which specify that all "plausible" confounders would have reduced the effect.

[e] Criterion not included in the formal GRADE framework and only applicable to observational studies.

Ratings of certainty should be clearly displayed in the GRADE table. For reductions in certainty levels, possible ratings include "none serious" (no downgrade), "serious" (downgrade by 1 level) or "very serious" (downgrade by 2 levels).

As an example, studies aiming to evaluate vaccine efficacy may be downgraded under the criterion of "indirectness" due to the use of surrogate end-points such as immunogenicity data used to measure vaccine efficacy.

For upgrading the certainty level, possible ratings include "not applicable" (no upgrade), "strong evidence" (upgrade by 1 level) or "very strong evidence" (upgrade by 2 levels). Final quality levels cannot exceed 4 or drop below 1. If there are major limitations in the study design commensurate with the design, then upgrading criteria should not be applied. Whenever a downgrade or upgrade is applied, a footnote is needed to explain the rationale for the change in rating.

In some cases, studies may not be downgraded, but footnotes should still be used to highlight potential issues. This promotes transparency and indicates to readers that the full range of issues has been considered.

When the GRADE criteria are applied, studies should not be repeatedly penalized for limitations already factored into their starting rating. As an example, a controlled observational study that enters into the rating system at a level 2 should not be further downgraded because it was not randomized. On the other hand, it would be appropriate for passive surveillance data of uncertain quality to be downgraded through application of relevant limiting factors.

The decision to downgrade or upgrade a body of evidence depends on individual judgement. While two individuals may agree on the study limitations during a review of the evidence, it may not be clear whether or not such limitations warrant a change in rating. Similarly, the amount of variation in results from multiple studies allowed before they are deemed inconsistent, may be contentious. These examples illustrate the subjective nature of the exercise, the importance of expert opinion in interpretation and assessment of the criteria, and the need to explain the thought process used throughout the evaluation, so that areas of agreement and disagreement are evident.

4.5 Evidence-to-decision tables

To increase transparency and systematically consider predefined criteria leading to recommendations, SAGE uses evidence-to-decision tables which are based on the DECIDE[2] framework for decision-making *(45, 46)*.

Evidence-to-decision tables support SAGE's key policy recommendations; they adopt a standard format, as shown in Annex 2. A hallmark of the tables is the aim to improve transparency in decision-making. Interested parties can follow the logic and processes that lead to a given conclusion, recommendation and/or guideline. Such a process also promotes useful dialogue and opportunities to reassess the evidence as required.

The evidence-to-decision table in Annex 2 contains the following elements: background information and the research question; the specific criteria to consider and the related judgements that are made for each criterion; research evidence to support each judgement; and additional information to justify the judgements and decisions made for each criterion. The criteria outlined in the table are the following:

- Problem statement;
- Benefits and harms of the options including certainty of the evidence;
- Values and preferences;
- Resource use;
- Equity;
- Acceptability; and
- Feasibility.

Further information on these criteria, as well as on the evidence underpinning criteria-specific judgements, is provided in Table 3.

Evidence-to-decision tables do not usually represent a comprehensive compilation of all available evidence; rather they provide a high-level summary of key data and publications. They also contain references to more comprehensive summaries of the research evidence (e.g. background documents or systematic reviews).

[2] Evidence-to-decision tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. See: www.decide-collaboration.eu/evidence-decision-etd-framework

Table 3. Evidence-to-decision tables: additional information on criteria and related evidence

Criteria	Additional information on criterion	Information on, and examples of, evidence that may inform the criterion
Problem statement	Health-care decisions require setting priorities on how best to use limited resources. When decisions on health systems or public health are being made, the number of people affected by the decision is an important consideration, as are issues such as severity, urgency and consequences, and whether or not the problem is recognized as a priority *(47)*. The magnitude of the problem posed by a disease may be informed by the number of cases that are vaccine-preventable. Priorities could be based on international health targets such as those outlined in the Immunization Agenda 2030 *(4)*.	Global surveillance data of vaccine-preventable diseases, accessible via the Immunization Dashboard *(48)*. Global surveillance of specific disease endpoints *(49)*.
Benefits and harms of the options, including certainty of the evidence	SAGE and its working groups should consider the evidence on benefits and harms of the options, as well as the certainty of evidence. These criteria are usually informed by data on vaccine efficacy, effectiveness, immunogenicity and vaccine safety that has been systematically collected and assessed.	Systematic/rapid review and GRADEing of evidence on key PICO questions.
Values and preferences	These criteria encompass the assessment of the importance assigned to specific health outcomes and the certainty or variability of the importance in the target population. In addition, values and preferences are judged around how much the desirable effects outweigh the undesirable effects. For immunization, this will encompass (variability in) views on the certainty and importance related to the vaccine-preventable	Quantitative or qualitative data may be considered to inform this criterion. Often, globally-representative relevant data cannot be identified in the published or grey literature. Should resources be available, SAGE may request data collection to inform this criterion. Otherwise, expert judgement

	health outcome and the weighing of potential benefits (effectiveness) and harms (safety) of a specific vaccine. Both should be elicited and included in the decision-making process.	may be sought, and must be clearly identified as such.
Resource use	Because resources are limited, SAGE is asked to also advise on the resource implications of an intervention (e.g. a new vaccine or new vaccine formulation) compared to an alternative (e.g. no vaccination or other vaccine). SAGE not only takes into consideration the cost of a vaccine, but also the resource implications for a health system (e.g. human resource needs for additional vaccination campaigns). In addition, SAGE considers the extent to which an option is cost–effective.	This criterion is often informed by modelling data (economic evaluation, cost–benefit and cost–effectiveness). If a full evaluation is not possible, SAGE may describe anticipated resource implications in a qualitative manner.
Equity	Vaccination policies may increase equity or reduce inequity. SAGE and its working groups are asked to consider how the intervention may affect equity.	Quantitative or qualitative data may be considered to inform this criterion. Should resources be available, SAGE may request data collection to inform this criterion. Otherwise, expert judgement may be sought, and must be clearly identified as such.
Acceptability	SAGE should consider the acceptability of options to key stakeholders (generally immunization managers) and to the target population. The acceptability of an option may depend on the evidence presented for some of the preceding criteria, such as the distribution and timing of harms, benefits and costs, ethical principles or judicial consequences.	Quantitative or qualitative data may be considered to inform this criterion. Should resources be available, SAGE may request data collection to inform this criterion. Otherwise, expert judgement may be sought, and must be clearly identified as such.

Feasibility	Feasibility can affect decisions about whether or not to recommend a vaccine-related intervention. Feasibility is influenced by many factors such as the resources available (e.g. sufficient health clinics or vaccinators); programmatic considerations (e.g. the possibility of integration into an existing vaccination schedule); the properties of the intervention (e.g. packaging or cold-chain requirements); the existing and necessary infrastructure; and training (e.g. training of health workers).	Quantitative or qualitative data may be considered to inform this criterion. Should resources be available, SAGE may request data collection to inform this criterion. Otherwise, expert judgement may be sought, and must be clearly identified as such.

The evidence-to-decision table concludes with the balance of consequences of benefits and harms, the recommendation and justification for the aforementioned recommendation, implementation considerations, and research priorities. SAGE generally provides one to two evidence-to-decision tables related to the main policy question(s). Additional tables may be required.

Based on the decision-making processes, the table may be amended to reflect SAGE's view on certain criteria and finalized reflecting the WHO recommendation. Evidence-to-decision tables are publicly accessible and published alongside the policy recommendations.

4.6 SAGE good practice statements

Good practice statements typically represent situations in which a large and compelling body of triangulated evidence, including several indirect comparisons and often composed of several bodies of evidence linked together in a causal pathway, unequivocally demonstrates the net benefit of the recommended action. These types of recommendations are then labelled as such.

Good practice statements represent recommendations that SAGE considers important, but not appropriate for formal ratings of certainty of evidence. They are a practical resource when SAGE has confidence that the benefits of a recommended vaccine/intervention clearly outweigh the harms.

Good practice statements are used when evidence may be indirect, difficult or resource-intensive; when collecting the indirect linked evidence supporting the recommendations would be onerous and unproductive; and when the potential to cause harm is low. However, a lack of resources or lack of time are insufficient reasons to support the development of a good practice statement when the use of GRADE would be more appropriate. SAGE aims to use good practice statements sparingly and whenever warranted will adopt formal grading of the evidence.

A set of guiding questions are used by SAGE to determine the need for a good practice statement.

Guiding questions particular to good practice statements:*
i) Is the message really necessary?‡
ii) After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences?
iii) Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?
iv) Is there a well-documented clear and explicit rationale connecting the linked, indirect evidence? §

*Modified from Guyatt et al 2016 *(50)*.
‡Original question: Is the message really necessary in regard to actual health-care practice?
§Original question: Is there a well-documented clear and explicit rationale connecting the indirect evidence?

The answers to all four questions should be "yes". To proceed with development, a good practice statement should be clear and actionable, as for all recommendations.

A good practice statement will be a WHO recommendation; however, it would differ from a WHO recommendation using the formal application of GRADE. Good practice statements will be identifiable through thorough documentation of the responses to the guiding questions. These will be published as a supporting document along with the specific WHO vaccine position paper.

SAGE will continuously monitor the applicability of the guiding questions to its good practice statements and adjust these in the future if necessary.

SAGE will give due consideration to neither overuse good practice statements nor trivialize these for common sense policy statements. Where ample previously graded evidence on specific recommendations is available, regrading statements or labelling them as good practice statements may not be necessary.

4.7 SAGE recommendations

4.7.1 Strength of the recommendations

In the formal GRADE approach, developed by the GRADE working group, a strength of recommendation score is given (e.g. "strong" versus "conditional" (formerly referred to as "weak")) *(51)*. In the context of immunization policies, SAGE follows this approach and provides countries with strong or conditional recommendations.

Strong recommendations may be issued when the evidence-base has been judged to be moderate to high. Strong recommendations may also be issued exceptionally based on low or very low certainty of evidence, if the intervention reduces mortality in life-threatening situations, or if adverse events following the intervention are deemed to be acceptable *(51)*.

Recommendations that are scored as strong, may either be for or against a certain intervention. They may also be restrictive to a certain condition, setting, geography or population.

Conditional recommendations may be issued when the evidence-base has been judged to be low to very low, or when there is a close balance between the desirable and the undesirable consequences of an intervention. As with strong recommendations, conditional recommendations may be restrictive to a certain condition, setting, geography or population.

WHO retains the right to not issue recommendations at a certain stage for various reasons, such as a lack of data, or the data quality being too low; however the situation will be reassessed in the future. WHO may also recommend shared clinical decision-making where the appropriateness of an intervention for an individual person should be discussed with the treating physician.

WHO recommendations will be identified and explained in the evidence-to-decision table. Standardized wording on the formulation of SAGE recommendations has been developed (see Annex 4).

4.7.2 Off-label recommendations

Initial vaccine label indications will be limited to the population tested in the clinical trials, where evidence supports the safety and efficacy of vaccine use. After the vaccine has entered the market, post-authorization data will become available at the request of the national regulatory authority (NRA) for the continued monitoring of safety and effectiveness. In addition, post-marketing studies may support an extension of the label indication to different population groups or use in different schedules or routes of administration. An evaluation of all available data, and a risk–benefit assessment conducted by public health advisory bodies, may result in public health recommendations that differ from the indications contained in the vaccine product label as per the market authorization granted by a NRA. Discrepancies may occur in settings where the vaccine has been authorized for a certain indication in a certain population with a specific schedule, while having been recommended for use by a public health advisory body for a different or extended indication and/or in a different target group within a population and/or with a different schedule. This would lead to a so called ‘‘off-label” public health use *(52)*.

Divergent marketing authorizations imply that vaccine labels may differ between countries. This is often a consequence of national policies and other criteria used in the NRA vaccine assessment. The assessment by the NRA of the benefit–risk balance will be based on national methods, standards and laws *(52)*. The same evidence may lead to a label indicating use in specific groups in one country, while another country’s regulatory body may have a different interpretation of the evidence and science and decide that the evidence is insufficient to approve the same vaccine for the labelled use in the same groups in their country.

SAGE may issue recommendations that are off-label in some or all countries. The importance of SAGE’s off-label recommendations is twofold: the recommendations provide global guidance to NITAGs to consider the public health benefit when going beyond the use-indication. SAGE may further set priorities and contribute to label extension efforts by NRAs and manufacturers.

Any guidance document containing recommendations on off-label use clearly states this in its introduction; it must also provide a standard WHO disclaimer on the use of off-label recommendations stating the following:

The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis and other factors,

as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

As the SAGE policy recommendations cannot be checked against all national marketing authorizations, they may be off-label in some settings and in line with the marketing authorization in others.

4.7.3 Research priorities

Beyond policy and strategic recommendations regarding public health programmes, SAGE, often informed by the evidence review conducted by the working group, is tasked to identify research gaps and advise WHO on the research priorities to prioritize items for future research agendas and encourage additional research in particular in support of additional or stronger immunization policy.

4.7.4 Criteria that underpin the development of SAGE recommendations, including gender, equity and human rights

The standards and principles relating to human rights guide all development and formulation of WHO recommendations, in line with the organization's core principles *(53)*. Gender-related barriers and gender inequality can prevent individuals from getting vaccinated *(54)*.

Gender mainstreaming is the process of assessing the implications for women, men, girls and boys of any planned action including legislation, policies or programmes at all levels *(55)*. It refers to a strategy for making the concerns and experiences of women and girls, men and boys, integral to the design, implementation, monitoring and evaluation of policies and programmes so that all can benefit equally, and inequality is not perpetuated.

The need for gender mainstreaming across the core principles and strategic priorities of IA2030 is paramount *(56)* to ultimately achieve the IA2030 vision: a world where everyone, everywhere, at every age benefits fully from vaccines for good health and well-being. Therefore, any strategic or policy advice given by SAGE is assessed in light of its implications for individuals of any gender. SAGE guidance aims to contribute to gender equity and ensure that every person has the same

opportunities to access and benefit from immunization services. In line with IA2030 priorities, the specific elements considered by SAGE in its deliberations are equitable coverage across individuals of any gender; understanding and addressing all direct and indirect barriers to access to immunization services, including those related to the gender of caregivers and health workers, and increasing the full and equal participation of women in decision-making at all levels.

5 The role of SAGE in relation to global (immunization) strategies

Strategies are an important step in the translation of policies into plans and action. At a global level, WHO produces or contributes to the development of strategies to provide momentum and direction for change at a global, regional or country level *(57)*.

Strategies may directly involve health services, which contribute to both improving health and managing disease. More often, however, strategies are multisectoral; they address the broader determinants of health, and involve an ecological perspective which requires cross-sectoral and multilevel engagement with a wide variety of stakeholders which impact on health, including social, economic and political actors *(57)*.

Often, strategies are developed "top-down" but, increasingly, organizations seek the early involvement of strategic partners and key stakeholders at various levels, such as civil society, governments and local communities. Strategies emerge from the grassroots of an organization; finding ways of integrating "top-down" with "bottom-up" is vital *(57)*. The IA2030 strategy was developed through a collaborative "bottom-up" co-creation process that engaged thousands of stakeholders around the world. This approach helped to ensure that the real needs of countries facing the greatest health inequalities were reflected. It also drew on lessons learned from the implementation of the Global Vaccine Action Plan (2011–2020) and disease-specific initiatives such as polio and measles eradication efforts *(4)*.

Strategies may be developed solely by WHO, or may represent the effort of multiple partners and constituencies, such as with the IA2030. The role of SAGE may depend on the breadth of the constituency of the strategy. SAGE may provide advice to WHO on subaspects of a strategy, or the strategy as a whole. With a global health strategy, for example, this may include the identification of needs, gaps and priorities; the assessment of feasibility and impact; and monitoring and evaluation.

For a global WHO health strategy:

- SAGE may advise WHO on the overall strategy and appraise the evidence that inform the strategy.

- SAGE may be asked to clarify and frame the public health problem or issue. For this, SAGE (and its working groups) may be asked to collect, analyse and synthesize the data or the historical context and information related to the strategy envisaged.
- SAGE may be asked to assess policy options for inclusion into a strategy based on criteria such as health impact, feasibility, acceptability, resource use and economics, and acceptability.
- SAGE will contribute to the strategy by developing evidence-based policy recommendations.
- SAGE may be asked to monitor progress in the implementation of the strategy.
- SAGE may be asked to serve as independent body to evaluate the process, impact and outcomes of the strategy.
- SAGE may use the evaluation results to inform the evidence base and feed into potential new strategies.

6 Development, publication and update of WHO vaccine position papers and other policy guidance

In accordance with its mandate to provide normative guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These contain WHO's detailed recommendations on a specific vaccine-preventable disease based on SAGE's advice.

6.1 WHO vaccine position paper development process

WHO vaccine position papers are published in the WHO Weekly Epidemiological Record (WER) *(13)*. The papers outline WHO's position on vaccines and combinations of vaccines against diseases or vaccine-related issues that have an international public health impact. Vaccine position papers are generally concerned with the use of vaccines in large-scale immunization programmes and outline strategic as well as policy guidance on the use of vaccines against a specific antigen. The position papers are intended for use mainly by national public health officials and managers of immunization programmes, as well as to provide information for national disease control programmes.

Vaccine position papers are drafted by the WHO disease focal point(s), based on the recommendations formulated by SAGE during plenary sessions, with input from additional WHO staff at WHO headquarters and regional levels. The papers summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of the vaccines worldwide, including recommendations on research priorities.

The Steering group on vaccination policy guidance provides final internal quality control to the development, publication and update of end products such as the WHO vaccine position papers. The group aims to ensure transparency, coherence and quality control by providing an independent evaluation of the scientific, technical and methodological aspects of the position papers and other vaccination policy. The group further appraises the feedback received from external peer-review.

The steering group is tasked with reviewing an initial draft of the WHO vaccine position paper and the related evidence assessments (GRADE and evidence-to-decision tables). Feedback received will be incorporated. After the initial draft has been refined it is subject to broad external peer-review. Reviewers include end-users and external subject-matter experts who have not been involved in the evidence review or the development of the policy, such as selected national

immunization managers, internationally renowned subject-matter experts, other interested parties and the vaccine industry. The request for peer-review from industry is channelled through the International Federation of Pharmaceutical Manufacturers Association (IFPMA) and the Developing Country Vaccine Manufacturer Network (DCVMN). The purpose of industry review is to ensure the adequate reflection of the current evidence around certain products as reflected in the background section. WHO does not consider any proposed changes by industry to the WHO position. SAGE and SAGE working group members are also given the opportunity to revise the final draft. The list of peer reviewers is available on request from the Executive Secretary for SAGE.

The WHO focal point compiles and assesses the feedback received from the external review and under the explicit direction of the steering group, produces a final draft of the paper. Final decisions on the inclusion of suggested feedback from peer-review lie with WHO. The finalized WHO vaccine position paper, along with the related systematic review(s), GRADE and evidence-to-decision tables, are published on the WHO website.

WHO vaccine position papers are updated when new data or novel products become available that impact the recommendations. The steering group further advises on the need to update the position papers or other vaccination policy guidance documents (such as GRADE and evidence-to-decision tables). A framework of criteria has been developed to facilitate the decision of the steering group as to whether a WHO vaccine policy update is required following the licensure of a new product (see Annex 3). Any decision on the need for an update is informed by the assessment of the steering group, although the final decision lies with WHO (Figure 2).

Figure 2. SAGE immunization policy cycle

6.2 Development of rapid advice and emergency response guidance

Decision-making under uncertainty is part of public health. Areas of uncertainty should be communicated transparently and honestly to policy-makers and the public. Issuing evidence-informed recommendations remains paramount, and communicating any limitations or uncertainties within an interim guidance is essential. In situations of urgent need, WHO may refer to SAGE for recommendations which may be required within a few days. Emergency or rapid advice guidance may be required when a rapid response is needed, most often in the context of a

PHEIC. In such situations, guidance may be issued on products that have not yet obtained full licensure or have WHO emergency use listing or NRA emergency use authorization only, as was the case for many COVID-19 vaccines. Guidance may further be required on licensed products, often for new indications or use-cases, such as with fractional dose use of yellow fever vaccine in an outbreak setting or the use of smallpox vaccines in response to the mpox outbreak. These types of guidance may further be issued when insufficient data are available for a formal recommendation and/or when there is considerable uncertainty around the available data. In addition, guidance may be issued in the context of a rapidly changing (epidemiological) situation where revisiting the published guidance within weeks or months is warranted. These types of guidance will be clearly identifiable and are always time-limited (from a few days to several months). An overview of the types of guidance is provided in Table 4.

6.2.1 Rapid advice guidance

Rapid advice guidance is published as **interim guidance** and is issued when there is an urgent need (i.e. within weeks to 3 months) for guidance on a question of uncertainty. The guiding principles of the evidence review process (see Methods for the development of WHO policy recommendations) remain when there is need for rapid advice guidance. It is important that careful review and consideration of the evidence should precede the development of recommendations, and that the entire process should be transparent, robust and reproducible. For the development of rapid advice, WHO aims to adhere to all critical steps required for issuing evidence-based recommendation as described above. However, there may be occasions where urgent and timely advice is required. At such times, modifications are acceptable at any of the stages outlined steps above to meet the accelerated timeline. The recommendations reflected in the rapid advice guidance are issued by SAGE in the context of an ordinary or an extraordinary SAGE meeting. On rare occasions, SAGE issues rapid advice guidance outside of these fora (e.g. in writing).

This content type will be reassessed to determine the need for updating at least every 3 months, more often continuously by the WHO Secretariat. Rapid advice guidance should be updated as soon as practicable if the methods used were less than standard or if new evidence emerges.

6.2.2 Emergency response guidance

Emergency response guidance is published as **emergency guidance** and is employed when there is an urgent need (i.e. within hours to days) for WHO’s guidance on a question of uncertainty. It

is important to note that there may be considerable restrictions to the evidence review processes. Furthermore, the involvement of SAGE in issuing recommendations may range from not being involved (i.e. WHO Secretariat guidance only), to minimal involvement (i.e. SAGE vetting the recommendations developed by the WHO Secretariat). Nevertheless, there will be transparent and explicit recording of decisions and rationale. This content type will be reassessed to determine the need for updating within 1 month – or more often continuously – by the WHO Secretariat. In this context, the WHO Secretariat may further determine the need to move from emergency guidance to rapid advice or regular SAGE guidance, based on available evidence and application of a more rigorous methodological assessment of the data.

Any rapid advice or emergency recommendations will be subject to SAGE review at the subsequent ordinary SAGE meeting. By that time SAGE will require a systematic assessment of literature and certainty of the evidence in support of specific recommendations. Based on this, SAGE may issue formal recommendations or determine that the evidence base may warrant the continuation of issuing interim recommendations.

A summary of WHO recommendations, rapid advice guidance and emergency response guidance is provided in Table 4.

Table 4. Summary of SAGE-related guidance

	Formal WHO recommendations	Rapid advice guidance	Emergence guidance
Title	"WHO vaccine position paper"	"Interim guidance"	"Emergency guidance"
Context	Outside of emergency, or public health emergency of international concern (PHEIC), stable (epidemiological) situation	PHEIC or other emergency, rapidly evolving (epidemiological) situation	Onset of PHEIC or other emergency, unclear or rapidly evolving (epidemiological) situation
Data availability	Data availability adequate for decision-making	Data with considerable limitations	No, or very limited, data
Methods	Standard processes of evidence-based decision-making + GRADE and Evidence to decision	Modifications at any step of evidence-based decision-making is acceptable to meet the accelerated timeline +/- GRADE and Evidence to decision	Evidence-informed as possible - GRADE and Evidence to decision
SAGE involvement	SAGE issues recommendation in Plenary meeting	SAGE issues recommendation in Plenary or Extraordinary meeting	Degree of SAGE involvement may range from not being involved (WHO Secretariat guidance) to minimal involvement (SAGE vetting)
Time	3 to 8 months	1 week to 3 months	Hours to days
Reassessment	Every 2 years; earlier if needed	Every 3 months; earlier if needed	Continuously

6.3 Implementation, adaptation, and evaluation

6.3.1 Publication, translation and dissemination

WHO vaccine position papers *(13)* are published in both English and French and subsequently translated into the remaining four official WHO languages (Arabic, Chinese, Russian and Spanish).

To avoid delays, interim recommendations are usually published on the WHO website. They are also translated into all official WHO languages.

SAGE guidance is disseminated through various channels such as:

- Press briefings
- The WHO website; the Global Immunization Newsletter *(58)* or TechNet *(59)*
- Promotion through the Global NITAG Network and the NITAG Resource Center *(60)*
- Presentations at RITAG, NITAG and other important immunization meetings
- Three-level WHO webinars for internal communication
- Distribution to key stakeholders via email distribution lists.

6.3.2 Implementation

Implementation is usually the responsibility of national immunization programmes guided by NITAGs. WHO headquarters, and WHO regional and country offices support implementation through various activities and the development of resources. A range of derivative documents or tools are developed to facilitate implementation. Implementation or operational research may be conducted to help inform field testing and rollout strategies to promote the uptake of recommendations.

The implementation of (new) vaccines in many countries would not be feasible without Gavi *(61)*. Gavi was set up as a Global Health Partnership in 2000, with the goal of creating equal access to new and underused vaccines for children living in the world's poorest countries. In particular, Gavi aims at accelerating access to vaccines, strengthening countries' health and immunization systems, and introducing innovative new immunization technology. Gavi works together with countries in scaling up domestically-funded immunization efforts. As countries develop economically, Gavi requires them to bear more of the costs until they can fully transition out of Gavi support.

6.3.3 Adaptation

RITAGs have been established in each of the six WHO regions – Africa, the Americas, the Eastern Mediterranean, Europe, South-East Asia and the Western Pacific. RITAGs are tasked with providing WHO Regional Directors and countries with recommendations on immunization priorities and strategies relating to regional epidemiological and social issues.

NITAGs are multidisciplinary groups of national experts responsible for providing independent, evidence-informed advice to national policy-makers and programme managers on policy issues related to immunization and vaccines.

Adaptation of SAGE guidance is carried out at regional as well as at national (or subnational) levels. WHO encourages the adaptation of global guidance by RITAGs and NITAGs, taking into account contextual circumstances such as local disease epidemiology, resource considerations and regional and national priorities.

The "GRADE-ADOLOPMENT" approach to guideline production combines adoption, adaptation, and, as needed, de novo development of recommendations. Using the structure of the GRADE evidence-to-decision frameworks, and the criteria that determine the direction and strength of a recommendation, allows users to create recommendations appropriate for their context. By using the evidence-to-decision criteria to present the research evidence and associated judgements transparently, regional and national advisory groups can facilitate the adoption of recommendations by others *(62)*.

6.3.4 Monitoring and evaluation

Vaccine monitoring and evaluation systems are used to collect and analyse data on vaccination coverage and other indicators, such as those related to the introduction of specific policies as recommended by WHO. WHO uses these data to obtain information on the impact of their vaccination policies.

In the context of the IA2030, the monitoring and evaluation (M&E) framework provides action-based indicators to monitor and evaluate progress toward IA2030 goals and strategic priority objectives. The M&E framework includes tailored indicators to enable the use of data for action to continuously improve immunization programmes at all levels. Underlying the three impact goals of IA2030, are seven impact goal indicators to monitor progress across country, regional and

global levels. The M&E framework provides strategic priority objectives and indicator options for regions and countries to inform the development of their own M&E frameworks *(63)*.

Since 1998, in an effort to strengthen collaboration and minimize the reporting burden, WHO and UNICEF have jointly collected information through a standard questionnaire – the Joint Reporting Form (JRF) – sent to all Member States. In 2021, the form was updated to a Cloud-based solution known as the electronic Joint Reporting Form (eJRF) *(48)*. The eJRF collects immunization data annually from countries which helps identify trends and gaps at the country, regional, and global levels. The data collected through the eJRF are reported cases of vaccine-preventable diseases globally, coverage of vaccination globally and over time, and other programme indicators (e.g. influenza vaccination policy).

The information collected in the eJRF serves as a critical resource for tracking implementation of SAGE-related strategies and policies worldwide. These data can help monitor improvements and identify gaps for evaluation.

7 Regulatory approval and prequalification/emergency use listing processes

WHO generally issues an evidence-based recommendation once a vaccine has received regulatory approval by an NRA of maturity level 3 or higher (for vaccine-producing countries); or when a vaccine is undergoing either WHO prequalification or emergency use listing (EUL); or when it is already prequalified or recommended for use under EUL. The processes leading to a recommendation for use and prequalification or EUL are independent.

While there is considerable overlap in the data requirements for policy, regulatory approval and prequalification, regulatory decision-making and immunization policy decision-making are distinct and independent.

The regulatory and prequalification processes involve determining the quality of a product; the consistency of manufacturing; and safety and efficacy, including relevant non-clinical data and programmatic suitability.

The policy process assesses the clinical data (safety, efficacy and effectiveness) from the perspective of the individual and also for population protection. It examines the context in which vaccination is to be introduced and determines which groups of people within the population would benefit most from the vaccine and with which schedule. In addition, the programmatic feasibility, equity and ethical considerations of vaccination are examined along with data on health economy.

7.1.1 Expert Committee on Biological Standardization

The WHO Expert Committee on Biological Standardization (ECBS) is tasked to provide recommendations and guidelines for the manufacturing, licensing and control of blood products and related in vitro diagnostic tests, biotechnology products and vaccines. The committee sets norms and standards for manufacturing, licensing and quality control to ensure the quality of vaccines and other biological products. These recommendations and guidelines are applied to the review of vaccines for prequalification.

In 2017, the ECBS updated their guideline on the regulatory expectations linked to the clinical evaluation of vaccines *(64)*.

7.1.2 National regulatory authorities

National regulatory authorities (NRAs) and national control laboratories are responsible for the regulatory oversight, testing and release of vaccines. Guidelines have been developed *(65)* for use

by NRAs, companies developing and holding licenses for vaccines, clinical researchers and investigators. The guidance takes into account the content of clinical development programmes, clinical trial designs, the interpretation of trial results, and post-approval activities; it also outlines the clinical assessment of immunogenicity, efficacy and effectiveness and safety data that require consideration by an NRA.

7.1.3 WHO prequalification

The WHO prequalification of vaccines is a service provided to UNICEF, other UN agencies and WHO Member States that procure vaccines. Many of these agencies make the procurement of vaccine products contingent on prequalification. The aim of prequalification is to ensure that vaccines used in immunization programmes are safe, efficacious, of consistent quality, and suitable for programmatic use. Prequalification also supports the specific needs of national immunization programmes as regards vaccine characteristics, such as potency, thermostability, presentation, labelling and shipping conditions. WHO also ensures the continued safety and efficacy of prequalified vaccines through regular re-evaluation, site inspection, targeted testing and investigation of any product complaints or adverse events following immunization.

Any manufacturer can apply for prequalification assessment of a vaccine provided that the vaccine:

- is included on the vaccines prequalification priority list;
- meets the mandatory characteristics for programmatic suitability;
- has received marketing authorization from the NRA of reference for prequalification, and for which the NRA responsible for its regulatory oversight is a of maturity level 3 or higher[3] for vaccine-producing countries.

NRAs and national control laboratories are critical to WHO vaccines prequalification programmes since they are responsible for regulatory oversight, testing and the release of WHO-prequalified vaccines.

While the WHO prequalification and policy processes are independent, WHO generally aims for a coordinated approach and consorted issuance of policy recommendations and WHO prequalification. In situations where a vaccine may not submitted for prequalification but is

[3] See WHO Regulation & Prequalification: www.who.int/teams/regulation-prequalification/regulation-and-safety.

approved by an NRA of maturity level 3 or higher (for vaccine-producing countries), WHO may issue policy recommendations if the product addresses a major unmet medical need.

7.1.4 WHO procedure for emergency use listing

The WHO Emergency Use Listing Procedure (EUL) is a risk-based procedure for assessing and listing unlicensed vaccines (as well as therapeutics and in vitro diagnostics) with the ultimate aim of expediting the availability of such products to people affected by a PHEIC declared by the WHO Director-General, or a graded emergency at global level. The listing procedure assists interested UN procurement agencies and Member States in determining the acceptability of using specific products, based on an essential set of available data on quality, safety, efficacy and performance, as well as programmatic suitability. The procedure is an important tool for companies wishing to submit their products for use during health emergencies.

For products to be considered eligible for emergency listing, the following criteria must be met:

- The disease for which the product is intended is serious or immediately life threatening, or has the potential to cause an outbreak, epidemic or pandemic.
- It is reasonable to consider the product for EUL assessment – e.g. there are no licensed products for the indication or for a critical subpopulation (e.g. children);
- Existing products have not been successful in eradicating the disease or preventing outbreaks.
- The product is manufactured in compliance with current good manufacturing practices.
- The NRA responsible for its regulatory oversight is of maturity level 3, or higher for vaccine-producing countries.
- The NRA responsible for its regulatory oversight has issued, at the least, an emergency use approval/authorization or equivalent.
- The applicant undertakes to complete the development of the product and applies for WHO prequalification once the product is licensed.

A WHO policy recommendation for use of vaccines in the context of a PHEIC depends on approval by a regulatory authority of maturity level 3 or higher, and/or WHO EUL.

8 Concluding remarks

Providing policy guidance on the use of vaccines and immunization-related topics in different geographical and cultural contexts is a challenging but important public health endeavour that must be founded on scientific evidence of the highest quality available.

The approaches described in this guidance represent the consensus of a range of immunization experts on how best to apply a rigorous approach to evaluating the quality of scientific evidence. As judgement will always be necessary in policy development, transparency is required throughout the process.

This document is intended to increase transparency and standardization of the development of WHO vaccine and immunization recommendations, and will continue to be regularly updated as improvements are identified and as the methodology evolves.

9 Resources

Type	Description	Reference
NITAG Resource Center	Resource centre on national immunization policies and global recommendations on vaccine-preventable diseases	www.nitag-resource.org
SYSVAC registry	The SYSVAC registry includes a variety of systematic reviews, including living, rapid and umbrella reviews, allowing users to search for reviews using free text and keywords (e.g. disease/pathogen, population). Reviews in the registry have been assessed for quality, using the AMSTAR 2 appraisal tool.	www.nitag-resource.org/sysvac-systematic-reviews
GRADE working group	Resources, publications, tools and training around the Grading of Recommendations Assessment, Development and Evaluation (GRADE)	www.gradeworkinggroup.org
TechNet-21	Global network of immunization professionals established by WHO and UNICEF in 1989, committed to strengthening immunization services by: • Building relationships • Sharing knowledge • Coordinating activities • Aligning priorities and goals	www.technet-21.org
Immunization dashboard	Database to monitor global trends and total numbers in reported cases of vaccine preventable diseases up to 2021. These data can help monitor improvements and identify gaps for evaluation. Data are reported annually through the WHO/UNICEF Joint Reporting Form on Immunization (JRF).	WHO Immunization Data portal - Global
Immunization and vaccines related implementation research advisory committee (IVIR-AC)	IVIR-AC is tasked with reviewing vaccine related quantitative methods and implementation research. Meeting reports and materials are available on the WHO website.	www.who.int/groups/immunization-and-vaccines-related-implementation-research-advisory-committee

Market information for access to vaccines (MI4A)	Resources related to market information for access to vaccines (MI4A vaccine purchase data; market studies; country case studies; and analysis on MI4A data use).	www.who.int/teams/immunization-vaccines-and-biologicals/vaccine-access/mi4a

References

1. Jenicek M. Epidemiology, evidenced-based medicine, and evidence-based public health. Epidemiology. 1997;7:187-97. doi: 10.2188/jea.7.187
2. Clark R, Haby M. Chapter 7. Evidence-based policy: why and how. In: Carey G, Landvogt K, Barraket J, editors. Creating and implementing public policy: cross-sectoral debates. Abingdon, Oxon: Routledge; 2015:98–112.
3. Brownson RC, Fielding JE, Maylahn CM. Evidence-based public health: a fundamental concept for public health practice. Annu Rev Public Health. 2009;30:175–201. doi: 10.1146/annurev.publhealth.031308.100134
4. Immunization Agenda 2030 (Immunization Agenda 2030 (who.int), accessed 8 March 2024).
5. Evidence, policy, impact: WHO guide for evidence-informed decision-making. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240039872, accessed 8 March 2024).
6. WHO handbook for guideline development, 2nd Edition. Geneva: World Health Organization; 2014 (https://www.who.int/publications/i/item/9789241548960, accessed accessed 8 March 2024).
7. Terms of Reference for the Strategic Advisory Group of Experts (SAGE) on Immunization (https://www.who.int/publications/m/item/sage-terms-of-reference, accessed 8 March 2024).
8. Strategic Advisory Group of Experts (SAGE) on Immunization members and biographies (Strategic Advisory Group of Experts on Immunization (who.int), accessed 8 March 2024).
9. SAGE working group on influenza. World Health Organization. (Strategic Advisory Group of Experts on Immunization (who.int), accessed 8 March 2024).
10. Code of conduct for responsible research (Code of Conduct for responsible research (who.int), accessed 8 March 2024).
11. SAGE Agenda-Setting Process (Strategic Advisory Group of Experts on Immunization (who.int), accessed 8 March 2024).
12. WHO Strategic Advisory Group of Experts on Immunization (SAGE). SAGE meetings. Geneva: World Health Organization (Strategic Advisory Group of Experts on Immunization (who.int), accessed 8 March 2024).
13. WHO Weekly Epidemiological Record (WER). Geneva: World Health Organization (The Weekly Epidemiological Record (WER) (who.int), accessed 8 March 2024).
14. WHO Declaration of Interests (Declarations of interest (who.int), accessed 8 March 2024).
15. Strategic Advisory Group of Experts (SAGE) on Immunization working groups (Strategic Advisory Group of Experts on Immunization (who.int)), accessed accessed 8 March 2024.
16. How WHO is funded. Geneva: World Health Organization; 2023 (How WHO is funded, accessed 8 March 2024).
17. WHO's engagement with non-State actors. Framework of Engagement with Non-State Actors (FENSA). Geneva: World Health Organization; 2023 (WHO's engagement with non-State actors, accessed 8 March 2024).

18. Richardson WS, Wilson MC, Nishikawa J, Hayward RSA. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995 Nov-Dec;123(3):A12-3. PMID: 7582737.
19. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. Journal of Clinical Epidemiology. 2011;64:395-400. doi: 10.1016/j.jclinepi.2010.09.012
20. Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training, accessed 8 March 2024).
21. Developing NICE guidelines: the manual (www.nice.org.uk/process/pmg20/chapter/introduction, accessed 8 March 2024).
22. Fernandes S, Jit M, Bozzani F, Griffiths UK, Scott JAG, Burchett HED. A bibliometric analysis of systematic reviews on vaccines and immunisation. Vaccine. 2018;36:2254-61. doi: 10.1016/j.vaccine.2018.02.049
23. Jo CL, Burchett H, Bastías M, Campbell P, Gamage D, Henaff L et al. Using existing systematic reviews for developing vaccination recommendations: Results of an international expert workshop. Vaccine. 2021;39:3103-10. doi: https://doi.org/10.1016/j.vaccine.2021.04.045.
24. WHO Global Advisory Committee on Vaccine Safety. Geneva: World Health Organization (Committee reports - GACVS (who.int), accessed 8 March 2024).
25. Tricco AC, Antony J, Zarin W, Strifler L, Ghassemi M, Ivory J et al. A scoping review of rapid review methods. BMC Medicine. 2015;13:224. https://doi.org/10.1186/s12916-015-0465-6
26. Garritty C, Gartlehner G, Nussbaumer-Streit B, King VJ, Hamel C, Kamel C et al. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. Journal of Clinical Epidemiology. 2021;130:13-22. doi: https://doi.org/10.1016/j.jclinepi.2020.10.007.
27. Simmonds M, Elliott JH, Synnot A, Turner T. Living Systematic ReviewsSystematic reviews. In: Evangelou E, Veroniki AA, editors. Meta-Research: Methods and Protocols. New York, NY: Springer US; 2022:121-34 Living Systematic Reviews | SpringerLink, accessed 8 March 2024).
28. Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Bergman H et al. Efficacy and safety of COVID-19 vaccines. Cochrane Database Syst Rev. 2022. doi: 10.1002/14651858.CD015477
29. Terms of Reference for the Immunization and vaccines related implementation research advisory committee (IVIR-AC), 25 February 2022 (Terms of Reference for the Immunization and vaccines related implementation research advisory committee (IVIR-AC) (who.int), accessed 8 March 2024).
30. den Boon S, Jit M, Brisson M, Medley G, Beutels P, White R et al. Guidelines for multi-model comparisons of the impact of infectious disease interventions. BMC Medicine. 2019;17:163. doi: 10.1186/s12916-019-1403-9
31. Market Information for Access to Vaccines (MI4A). Geneva: World Health Organization; 2023 (www.who.int/teams/immunization-vaccines-and-biologicals/vaccine-access/mi4a, accessed 8 March 2024).
32. RoB 2: a revised Cochrane risk-of-bias tool for randomized trials (https://methods.cochrane.org/risk-bias-2, accessed accessed 8 March 2024).

33. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (https://drive.google.com/file/d/19R9savfPdCHC8XLz2iiMvL_71lPJERWK/view, accessed 2 February 2023).
34. Flemyng E, Moore TH, Boutron I, Higgins JPT, Hróbjartsson A, Nejstgaard CH et al. Using Risk of Bias 2 to assess results from randomised controlled trials: guidance from Cochrane. BMJ Evidence-Based Medicine. 2023:bmjebm-2022-112102. doi: 10.1136/bmjebm-2022-112102
35. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). C*ochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. (Chapter 25: Assessing risk of bias in a non-randomized study | Cochrane Training, accessed 8 March 2024) .
36. ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) (ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions - PubMed (nih.gov), accessed 8 March 2024).
37. ROBINS-I detailed guidance (2016) (Risk of bias tools - ROBINS-I detailed guidance (2016), accessed 8 March 2024).
38. Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. Journal of Clinical Epidemiology. 2016;69:225-34. doi: https://doi.org/10.1016/j.jclinepi.2015.06.005.
39. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. doi: 10.1136/bmj.j4008
40. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924. doi: 10.1136/bmj.39489.470347.AD
41. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401-6. doi: 10.1016/j.jclinepi.2010.07.015
42. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol. 2019;111:105-14. doi: 10.1016/j.jclinepi.2018.01.012
43. GRADE series Journal of Clinical Epidemiology (https://training.cochrane.org/online-learning/cochrane-methodology/grade-approach/jce-series, accessed 8 March 2024).
44. Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ. 1998;316:989. doi: https://doi.org/10.1136/bmj.316.7136.989.
45. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016. doi: 10.1136/bmj.i2016
46. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent

approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016;353:i2089. doi: 10.1136/bmj.i2016
47. Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, Flottorp S et al. The GRADE Evidence to decision (EtD) framework for health system and public health decisions. Health Res Policy and Syst. 2018;16:45. doi: 10.1186/s12961-018-0320-2
48. Immunization dashboard. Data reported annually through the WHO/UNICEF electronic Joint Reporting Form (eJRF) (Immunization, Vaccines and Biologicals (who.int), accessed 8 March 2024).
49. WHO International Agency for Research on Cancer Global Cancer Observatory (https://gco.iarc.fr/, accessed 8 March 2024).
50. Guyatt GH, Alonso-Coello P, Schünemann HJ, Djulbegovic B, Nothacker M, Lange S et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol. 2016;80:3-7. doi: 10.1016/j.jclinepi.2016.07.006
51. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66:726-35. doi: 10.1016/j.jclinepi.2013.02.003
52. Neels P, Southern J, Abramson J, Duclos P, Hombach J, Marti M et al. Off-label use of vaccines. Vaccine. 2017;35:2329-37.
53. Constitution. Geneva: World Health Organization (Constitution of the World Health Organization (who.int), accessed 8 March 2024).
54. Gender and immunization. Geneva: World Health Organization (Immunization, Vaccines and Biologicals (who.int), accessed 8 March 2024).
55. Report of the economic and social council for 1997. New York: UN Women; 1997 (Report of the Economic and Social Council for 1997., accessed 8 March 2024).
56. Why gender matters: Immunization Agenda 2030 (https://www.who.int/publications/i/item/9789240033948, accessed 8 March 2024.
57. Griffiths S, Fenton KA. Strategies and structures for public health interventions. Oxford University Press; 2021: 0 (https://doi.org/10.1093/med/9780198816805.003.0100, accessed 8 March 2024).
58. Immunization, Vaccines and Biologicals. Global Immunization Newsletter (GIN). Geneva: World Health Organization (Immunization, Vaccines and Biologicals (who.int), accessed 8 March 2024).
59. TechNet-21. The Technical Network for Strengthening Immunization Services. Geneva: World Health Organization (Home - TechNet-21, accessed 8 March 2024).
60. NITAG Resource Center (Home | NITAG RESOURCE CENTER (nitag-resource.org), accessed 8 March 2024).
61. Gavi. The Vaccine Alliance. (Gavi, the Vaccine Alliance, accessed 8 March 2024).
62. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. Journal of Clinical Epidemiology. 2017;81:101-10. doi: https://doi.org/10.1016/j.jclinepi.2016.09.009.
63. IA2030 Monitoring & Evaluation (M&E) Framework. Geneva: World Health Organization; 2020

(https://www.immunizationagenda2030.org/images/documents/IA2030_Annex_FrameworkForActionv04.pdf, accessed 8 March 2024).

64. WHO Technical Report Series 1004, Annex 9, 2017. Guidelines on clinical evaluation of vaccines: regulatory expectations. Geneva: World Health Organization (Guidelines on clinical evaluation of vaccines: regulatory expectations (who.int), accessed 8 March 2024).

Annex 1. WHO Declaration of interests form (vaccine-specific)

Version: April 2024

DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who **may have interests related to their expertise.** To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a **potential conflict of interest** (i.e. any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). In this declaration of interest (DOI) form, you must disclose any financial, professional or other interest relevant to the subject of the work or meeting which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of them, the relevant interests of other parties with whom you have substantial common interests (e.g. employer, close professional associates, administrative unit or department) and which may be perceived as unduly influencing your judgement.

Please complete this form and submit it to the WHO Secretariat at least 4 weeks, but no later than 2 weeks, before the meeting or work. You must also promptly inform the Secretariat of any change to this information prior to, or during the course of, the meeting or work. All experts must complete this form before their participation in a WHO activity can be confirmed.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your responses will be reviewed by the WHO Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, time frame and duration of the interest).

The Secretariat may conclude that no potential conflict exists, or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of three measures for managing the conflict of interest may be applied: the Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e. you will be excluded from the specific part of the meeting or work related to the declared interest and from the corresponding decision-making process); or (iii) mandates total exclusion (i.e. you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity and you will be asked if there have been any changes in your circumstances since completing the DOI form. A summary of all declarations and actions taken to manage any declared interests will be **published** in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside of WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing and signing this DOI form signifies that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

Name:
Institution:
Email:

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):

_____

Please answer each of the questions below. If the answer to any of the questions is "Yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e. spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, industry association, research institution, or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

1. VACCINE- AND IMMUNIZATION-RELATED INTERESTS

Within the **past 4 years**, have you had any **vaccine- or immunization-related interests** of financial and/or intellectual nature that you need to declare?
Such interests could encompass research support, other remuneration from a commercial or non-commercial entity, investment interests, intellectual property rights or interests expressed in public statements and positions, generation of data that will be subject of the meeting, advisory functions or others. Please note, that the term unit/organization refers to the entity led by the expert, including staff directly supervised by the expert. It is not necessary to declare funding going to co-workers working on project unrelated to the expert's engagements.

☐ YES	☐ NO
If "YES", please specify below in Nos 1.1–1.6.	*If "NO", please go to No 2: NON- VACCINE- AND NON-IMMUNIZATION-RELATED INTERESTS.*

No 1.1 Patents, stocks and licenses. Within the **past 4 years**, have you or one of your close relatives owned patents, stocks, bonds, stock-options or licenses related to vaccines, vaccine-related products or products for prophylaxis of vaccine-preventable diseases?

☐ YES ☐ NO

If yes, please specify.

Type of interest	Name of company, organization, or institution	Belongs to:	Is the amount of income or value of interest financially significant (i.e. US$ ≥5000)?	Current interest (or year ceased)?
		☐ You ☐ Family member ☐ Employer ☐ Research unit ☐ Other *If other, please specify*:	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If No, year ceased:*
		☐ You ☐ Family member ☐ Employer ☐ Research unit ☐ Other *If other, please specify*:	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If No, year ceased:*

No 1.2 Committees and boards. Do you currently serve, or have you, within the **past 4 years**, served on a commercial or non-commercial immunization-related advisory committee or board (e.g. scientific advisory board; supervisory board; data and safety monitoring board)?

☐ YES ☐ NO

If yes, please specify.

Type and name of committee	Function	Funding going to self or to unit?	Is the amount of income or value of interest financially significant i.e. US$ ≥5000)?	Current interest (or year ceased)?
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If No, year ceased:*

No 1.3 Consulting and advisory work. Do you currently serve or, during the **past 4 years,** have you served as an individual adviser or a consultant on a vaccine- or immunization-related topic (not related to a specific committee or board (see No 1.2), for a commercial or non-commercial entity (e.g. direct consulting to a pharmaceutical company, the government, etc.)?

☐ YES ☐ NO

If yes, please specify.

Topic	Employer/ source of funding	Funding going to self or to unit?	Is the amount of income or value of interest financially significant i.e. US$ ≥5000)?	Current interest (or year ceased)?
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*

No 1.4 Benefits from commercial entity. During the **past 4 years,** have you given any speech at an industry-organized and/or industry-funded symposium/conference; or have you organized a meeting, training or conference on a vaccine- or immunization-related topic sponsored or co-sponsored by a commercial entity for which you or your unit/organization have **directly received remuneration from a commercial entity**? Have you received or will you receive vaccine- or immunization-related benefits (travel grants, publication fee, gifts, etc.) from a commercial entity?

☐ YES ☐ NO

If yes, please specify.

Topic and type of interest	Source of funding	Funding going to self or to unit?	Is the amount of income or value of interest financially significant (i.e. US$ ≥5000)?	Current interest (or year ceased)
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
		☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*

No 1.5 Vaccine trials. During the **past 4 years**, have you or a staff member within your unit participated in, or conducted, a vaccine (-related) trial or prophylaxis product trial?

☐ YES ☐ NO

If yes, please specify.

Topic and type of trial	Specific role (investigator, principal investigator, supervisor or staff being investigators, etc.)	Source of funding	Funding going to self or to unit?	Is the amount of income or value of interest financially significant (i.e. US$ ≥5000)?	Current interest (or year ceased)
			☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*

			☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 USD ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
			☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
			☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
			☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*
			☐ Unit / Organization ☐ Self	☐ US$ >5000 ☐ US$ 0–5000 ☐ No income at all	☐ Yes ☐ No *If no, year ceased:*

No 1.6 Other. For any other vaccine- and immunization-related interests undertaken within the **past 4 years**, please describe the subject, specific circumstances, parties involved, time frame and other relevant details. If applicable, please specify the time frame and whether the interest was financially significant (i.e. US$ ≥5000) and who was the recipient of the funding. *PLEASE LIST ALL OTHER VACCINE-RELATED ACTIVITIES/RESEARCH/ENGAGEMENTS NOT COVERED IN THE ITEMS ABOVE.*

2. NON-VACCINE- AND NON-IMMUNIZATION-RELATED INTERESTS

Within the past **4 years**, have you had any **non-vaccine- or non-immunization-related interests**, financial and/or intellectual, that you need to declare?
These interests could encompass research support, remuneration from a commercial or non-commercial entity, investment interests, intellectual property rights, interests expressed in public statements and positions, or the generation of data that will be subject of the meeting, advisory functions or others**.**

☐ YES	☐ NO
If "YES", please specify below in Nos 1a–7.	*If "NO", please go to the last page to sign and finalize the form.*

EMPLOYMENT AND CONSULTING ***Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?***		
1a	Employment	☐ YES ☐ NO
1b	Consulting, including service as a technical or other advisor?	☐ YES ☐ NO
RESEARCH SUPPORT ***Within the past 4 years, have you, or has your research unit, received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?***		
2a	Research support, including grants, collaborations, sponsorships, and other funding?	☐ YES ☐ NO
2b	Non-monetary support valued at more than US$ 1000 overall (including equipment, facilities, research assistants, paid travel to meetings, etc.)?	☐ YES ☐ NO

	Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?	
INVESTMENT INTERESTS ***Do you have current investments (valued at more than US$ 5000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.***		
3a	Stocks, bonds, stock options, other securities (e.g. short sales)?	☐ YES ☐ NO
3b	Commercial business interests (e.g. proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)?	☐ YES ☐ NO
INTELLECTUAL PROPERTY ***Do you have any intellectual property rights that may be enhanced or diminished by the outcome of the meeting or work?***		
4a	Patents, trademarks, or copyrights (including pending applications)?	☐ YES ☐ NO
4b	Proprietary know-how in a substance, technology or process?	☐ YES ☐ NO
PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)		
5a	As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony related to the subject of the meeting or work for a commercial entity or other organization?	☐ YES ☐ NO
5b	Have you held an office or position, paid or unpaid, where you represented the interests of, or defended a position related to, the subject of the meeting or work?	☐ YES ☐ NO
ADDITIONAL INFORMATION		
6a	If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?	☐ YES ☐ NO

6b	To your knowledge, would the outcome of the meeting or work benefit, or adversely affect, the interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?	☐ YES ☐ NO
6c	Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work?	☐ YES ☐ NO
6d	Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work?	☐ YES ☐ NO
6e	Is there any other aspect of your background or present circumstances that is not addressed above and that might be perceived as affecting your objectivity or independence?	☐ YES ☐ NO
7.	**TOBACCO OR TOBACCO PRODUCTS** (answer without regard to relevance to the subject of the meeting or work) Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products, or that represents the interests of any such entity?	☐ YES ☐ NO

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is **"yes", check above and briefly describe the circumstances on this page. <u>If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.</u>**

Nos. 1–4: **Type of interest, question number and category (e.g. Intellectual property: 4.a Copyrights) <u>and</u> basic descriptive details.**	**Name of company, organization, or institution**	**Belongs to you, a family member, employer, research unit or other?**	**Amount of income or value of interest (if not disclosed, is assumed to be significant)**	**Current interest (or year ceased)**

Nos. 5–6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details				

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I shall promptly notify the WHO staff responsible and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself, and through the period up to the publication of the final results or completion of the activity concerned.

Date: _____ Signature_____

Annex 2. Strategic Advisory Group of Experts (SAGE) on Immunization: Evidence-to-decision framework*

<table>
<tr><td colspan="6">Evidence-to-decision framework
Question:
Population:
Intervention:
Comparison(s):
Outcome:</td></tr>
<tr><td colspan="6">Background:</td></tr>
<tr><td></td><td>CRITERIA</td><td colspan="3">JUDGEMENTS</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL INFORMATION</td></tr>
<tr><td>PROBLEM</td><td>Is the problem a public health priority?</td><td>No
☐</td><td>Un-certain
☐</td><td>Yes
☐</td><td>Varies by setting
☐</td><td></td><td></td></tr>
<tr><td>BENEFITS & HARMS OF</td><td><u>Benefits of the intervention</u>
Are the desirable anticipated effects large?</td><td>No
☐</td><td>Un-certain
☐</td><td>Yes
☐</td><td>Varies
☐</td><td></td><td></td></tr>
</table>

	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☐			
	Balance between benefits and harms	*Favours inter-vention* ☐	*Favours com-parison* ☐	*Favours both* ☐	*Fav-ours neith er* ☐	*Unclear* ☐		
	What is the overall quality of this evidence for the critical outcomes?	Efficacy/effectiveness of the intervention						
		No included studies	*Very low*	*Low*	*Mod - erate*	*High*		
		☐	☐	☐	☐	☐		
		Safety of the intervention						
		No included studies	*Very low*	*Low*	*Mod - erate*	*High*		
		☐	☐	☐	☐	☐		
VALUES & PREFEREN	How certain is the relative importance of the desirable	*Important uncertainty or variability*	*Possi bly impor tant uncert ainty*	*Probably no important uncertainty or variability*	*No impor tant uncert ainty or*	*No known undesirable outcomes*		

	and undesirable outcomes?		*or varia bility*		*varia bility*			
		☐	☐	☐	☐	☐		
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No*	*Prob-ably No*	*Un-certain*	*Probably Yes*	*Yes*	*Varies*		
		☐	☐	☐	☐	☐	☐		
RESOURCE USE	Are the resources required small?	*No*		*Uncertain*		*Yes*	*Varies*		
		☐		☐		☐	☐		
	Cost–effectiveness	*No*		*Uncertain*		*Yes*	*Varies*		
		☐		☐		☐	☐		
EQUITY	What would be the impact on health inequities?	*In-creased*		*Uncertain*		*Reduced*	*Varies*		
		☐		☐		☐	☐		

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health; immunization managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐		
	Which option is acceptable to target group?	*Inter-vention* ☐ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐		
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☐		
Balance of consequences		Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐
		Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	

Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)				
Implementation considerations				
Monitoring and evaluation				
Research priorities				

* This Evidence-to-decision table is based on the DECIDE Evidence to Decision (EtD) framework. See: www.decide-collaboration.eu/evidence-decision-etd-framework

Annex 3. Framework for policy similarity assessment

Framework for policy similarity			
Are the characteristics of the new vaccine product sufficiently similar to those covered by the current vaccine policy recommendation?			
Problem statement			
• Outline the problem statement • Identify product, time of assessment and context • Provide key references (e.g. publications and PQ* assessment report)			
Essential considerations			
Criteria	**Current policy**	**Data on product under consideration for policy inclusion**	**Justification for/against policy similarity**
Public health priority			
• Does the new product address the public health priority for which the current policy was developed?			
Benefits and harms of the intervention			
Mode of protection			
• Is the assumed mode of protection similar to that of the group of products recommended for the current policy (e.g. targets same antigens/life-cycle stage)?			
Target population			
• Can the new product be used in the same indication groups (or subset) as the current policy outlines?			
Off-label recommendation			

• Does the new product introduce any new off-label use compared to the group of products considered for the current policy?			
Indication for use			
• Is the indication for use of the new product the same as, or sufficiently similar to, that for the products that were reviewed to develop the current policy?			
Dosing requirements			
• Is the number of doses required for the specific indication (primary and potential booster doses) of the new product similar to the products that were reviewed to develop the current policy?			
Dosing schedule and route of administration			
• Are the dosing schedule (age of administration) and route of administration sufficiently similar; or is there flexibility in the dosing schedule of the new product to ensure that it falls under the current policy?			
Immunogenicity, efficacy and/or effectiveness			
• Does the new product have similar immunogenicity, efficacy and/or effectiveness to the group of products			

recommended under the current policy.			
Duration of protection			
• Do the data on the new product indicate similar duration of protection; or if there are no data, is there any reason to believe that the characteristics of the product's duration of protection may differ from the group of products recommended under the current policy?			
Reactogenicity			
• Is the reactogenicity profile comparable to the group of products recommended under the current policy?			
Serious adverse events			
• Is the safety profile comparable to the group of products considered under the current policy?			
Adverse events of special interest			
• Did any new adverse events of special interest emerge that had not been observed for the group of products recommended under the current policy?			
Safety in special populations (e.g. pregnant persons; malnourished children; other			

immunocompromised or HIV-positive individuals)			
• Is the safety profile comparable to the group of products recommended under the current policy?			
Adjuvant safety profile			
• Is the safety profile of adjuvants or other constituents comparable to the group of products recommended under the current policy?			
Concurrent and/or co-administered vaccines			
• Are the co-administration properties of the new product (assumed to be) sufficiently similar to those of the group of vaccines recommended in the current policy?			
Certainty of the evidence			
• Is the certainty of evidence adequate?			
Other considerations			
Resource-use, cost–effectiveness, equity, acceptability, feasibility or other criteria			
• Are there other important considerations in relation to the criteria above or to anything else which may			

impact on policy similarity (e.g. require a policy update)?	

OVERALL DECISION

- **Are the new vaccine characteristics and data similar to/adequately covered by the current vaccine policy recommendation?**

JUSTIFICATION FOR DECISION

*PQ = Prequalification

Annex 4. WHO standardized wording by scenario

Strength of recommendation	Evidence base	Direction of recommendation	Wording WHO SAGE recommendation	Explanation
STRONG	 Moderate–High*	Strong recommendation for	« WHO recommends […] »	WHO recommends that all countries worldwide introduce the vaccine/intervention/schedule into their routine immunization programmes.
	 Moderate–High*	Strong recommendation against	« WHO does not recommend […] »	WHO does not recommend that countries introduce the vaccine/intervention/schedule into their routine immunization programmes.
	 Moderate–High*	Strong recommendation for [setting]	« WHO recommends […] in certain settings »	WHO recommends that all affected countries introduce the vaccine/intervention/schedule into their routine immunization programmes in geographical locations where the targeted disease is recognized as a public health priority.
	 Moderate–High*	Strong recommendation for [subpopulation]	« WHO recommends […] in certain subpopulations. »	WHO recommends that all affected countries introduce the vaccine/intervention/schedule into their routine immunization programmes in certain populations.
	 Moderate–High*	Strong recommendation for [prerequisites]	« WHO recommends […] if certain conditions are met. »	WHO recommends that all affected countries introduce the vaccine/intervention/schedule into their routine immunization programmes if a certain condition is met (e.g. seropositivity).

*Except in settings where the quality of evidence is "Low" or "Very Low", but the intervention may reduce mortality in a life-threatening situation and adverse events are deemed to be acceptable (see: *(51)*).

Strength of recommendation	Evidence base	Direction of recommendation	Wording WHO SAGE recommendation	Explanation
CONDITIONAL (WEAK)	 Low–Very low	Conditional recommendation for	« WHO recommends that programmes may consider […] »	WHO recommends the intervention, but has limited confidence that the effect estimate lies close to the true effect.
	 Close balance between desirable and undesirable consequences	Conditional recommendation for	« WHO recommends that programmes may consider […] »	Benefits and harms may be closely balanced. WHO does not strongly recommend the vaccine/intervention/schedule; however, the benefits and other criteria considered by WHO (Evidence-to-decision) slightly favour the intervention.
	 Low–Very low or close balance between desirable and undesirable consequences	N/A	« WHO does not issue a recommendation at this stage. »	WHO is not in a position to issue a recommendation for various reasons (e.g. lack of data, data quality too low). Once the underlying issue is resolved, WHO will reconsider.
	 Low–Very low	Conditional recommendation for	« […] should be discussed with the treating physician. »	Shared clinical decision-making.

Department of Immunization, Vaccines, and Biologicals (IVB)

World Health Organization

20 Avenue Appia

1211 Geneva 27

Switzerland

9789240090729