Evidence to recommendations for COVID-19 vaccines: Evidence framework

A framework to inform the assessment of evidence and formulation of subsequent COVID-19 vaccine recommendations

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World Health Organization

Background

As countries prepare for the implementation of their respective coronavirus disease 2019 (COVID-19) vaccination programmes, the Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) is undertaking a three-step process to provide guidance for overall programme strategy as well as vaccine-specific recommendations.

Step 1: A Values Framework. The *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination* (1), was deliberated by SAGE on 26 August 2020 and issued on 14 September 2020. It outlines the general principles and public health objectives for vaccination. SAGE recommended that COVID-19 vaccine public health strategies should be grounded in ethical values as outlined in the Values Framework.

Step 2: Roadmap for prioritizing uses of Covid-19 vaccines (Prioritization Roadmap). The *WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply* (2), was deliberated by SAGE on 7 October 2020 and endorsed by WHO on 9 October 2020. To support countries in planning, the Prioritization Roadmap suggests public health strategies and target priority groups for different levels of vaccine availability and epidemiologic settings. The Roadmap will be updated, as necessary, to accommodate the dynamic nature of the pandemic and evolving evidence about vaccine impact.

Step 3: Evidence Framework (this document) to support development and issuing of vaccine-specific recommendations. As market-authorized vaccines become available and meet essential requirements as per WHO's target product profile (3), specific recommendations for the use of these vaccines will need to be issued. SAGE proposed the following framework for considering initial data emerging from clinical Phase III trials.

Rationale

While any recommendation on COVID-19 vaccines proposed by SAGE will be rooted in the methodology described below for developing evidence-based recommendations, the unprecedented speed of vaccine development, use of novel technological vaccine platforms, diversity of products, limited initial vaccine supply, as well as the pandemic nature of the disease, a Public Health Emergency of International Concern declared under the International Health Regulations, and resulting urgency for policy recommendations, require an expedited and tailored process for considering data emerging from COVID-19 vaccine trials.

This Evidence Framework outlines the principles and processes that will guide SAGE in reviewing the available evidence on specific vaccine products and platforms and ultimately assist in developing COVID-19 vaccination recommendations.

This Evidence Framework for considering vaccine-specific recommendations builds on the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination* as well as on the *WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply*. The Values Framework articulates the overall goal of COVID-19 vaccine deployment. It provides six core ethical principles that should guide distribution and twelve objectives that further specify these principles. The Roadmap builds on the population subgroups identified in the Values Framework and serves as guidance on preparing for vaccine prioritization decisions within countries. It considers and ranks priority groups for vaccination based on epidemiologic settings and vaccine supply scenarios

Guiding principles

The following considerations guided the development of this Evidence Framework:

- This Evidence Framework must remain fully aligned with the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination* as well as the *WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply* that preceded it.
- Any product to be considered for use through this Evidence Framework should have obtained (or is simultaneously obtaining) WHO prequalification status, WHO Emergency Use Listing and/or (emergency) approval by a stringent regulatory authority[1] and is available in sufficient supply for international distribution.
- Critical, product-specific, (interim) Phase III trial data required for policy-making (further described below) are available.

SAGE methodology for evidence-based recommendations

SAGE and its Working Groups apply the principles of evidence-based recommendation-making. SAGE requires that its policy development processes are based on systematic retrieval, synthesis and quality assessment of the best available evidence in support of the recommendations proposed to WHO.

A detailed description of SAGE and its Working Groups' methods, including information on the GRADE and the evidence-to-recommendation tables used, can be found in the "Guidance for the development of evidence-based vaccination recommendations."(4)

For its review of evidence, SAGE requires that its critical questions are formulated using the **P**opulation, **I**ntervention, **C**omparison and **O**utcome (PICO) approach.

Beyond a living systematic review of literature and in this case, review of other data sources, such as clinical study reports, risk of bias assessments of the retrieved evidence and Grading of Recommendations Assessment, Development and Evaluation (GRADE) to determine the overall quality of the body of evidence are conducted. As outlined in the SAGE guidance document for issuing evidence-based recommendations, GRADE does not need to be applied to the entire evidence, though it is required for certain critical outcomes on vaccine efficacy, safety and duration of protection.

SAGE and its Working Groups' deliberations on recommendations are guided by the GRADE DECIDE evidence-to-recommendation table (Annex 1), which lists explicit criteria beyond the benefits and harms of a specific intervention, such as acceptability, feasibility, equity, health systems and financing considerations specific to guide the formulation of recommendations.

GRADE DECIDE evidence-to-recommendation tables are required for key recommendations to ensure transparency of the process by listing the critical evidence in support of a recommendation and by reflecting the considerations proposed by the panel members.

The Working Group assembled the "Compendium of critical evidence questions for COVID-19 policy making" (5) which lists relevant questions, structured by criterion as outlined in the SAGE evidence-to-recommendation table, for which evidence will be important to formulate recommendations for consideration by WHO regarding the use of COVID-19 vaccines as they become available. These criteria include:

Criterion: Benefits & Harms of the Intervention

Criterion: Values & Preferences

Criterion: Resource Use

Criterion: Equity

Criterion: Acceptability

Criterion: Feasibility

Process for development of the Evidence Framework

This Evidence Framework focuses on assessing the data and evidence in relation to the Criterion: Benefits & Harms of the Intervention.

An iterative process for agreeing on the Evidence Framework was used in consultation with all members of the Working Group on COVID-19 Vaccines (6), which includes the Chairs of other WHO immunization advisory committees as well as Chairs of the Regional Immunization Technical Advisory Groups (RITAGs) of all 6 WHO regions. After detailing the process within the evidence and the prioritization subgroup of the SAGE Working Group, it was presented to the full SAGE Working Group which approved the process.

[1] WHO Regulations. https://www.who.int/medicines/regulation/sras/en/, accessed Nov 2020

Type of vaccine-specific data considered, retrieval and quality assessment

Initially, SAGE will consider relevant data stemming from randomized controlled Phase III trials. Earlier phase I-II immunogenicity and safety data will be considered in support of certain recommendations if required. As further evidence emerges in the future from alternative clinical trial designs or from observational studies, SAGE will take this into consideration, while acknowledging the quality of the observational evidence being lower than from randomized controlled trials.

For the evidence retrieval, SAGE will be supported by a living systematic mapping and living evidence synthesis of Phase III trial publications led by Cochrane France. All studies will be evaluated for potential bias using Cochrane risk of bias criteria and graded using the GRADE approach.(7;8) 'Summary of findings' tables will be prepared to present estimated relative and absolute risks.

A protocol for this living review of evidence will soon be available on the related website (https://covid-nma.com/vaccines/).

Given the urgency of issuing policy recommendations, which needs to occur in parallel or shortly after (emergency use) licensure of a product, SAGE will consider unpublished data provided to WHO by the manufacturer, granted that these data, as relevant for policy recommendation, will become available in the public domain as soon as the product is licensed.

In particular at the early stages of vaccine licensure and use, there will be limited data, e.g., on vaccine use in certain subpopulations or for certain outcomes.

Given the public health relevance of these vaccines, SAGE may nevertheless be required to issue policy recommendations based on indirect or incomplete data or on expert judgment where data are not yet available. The GRADE and evidence-to-recommendation tables will assist with transparently laying out the quality of data and the data gaps.

Developing critical evidence questions for policy recommendations

The following population, intervention, comparison and outcome (PICO) questions build on the Compendium of research questions, the Prioritization Roadmap and Values Framework.

Population

The target populations were extracted from the Prioritization Roadmap which laid out target populations by epidemiological and supply scenario (Annex 1,2,3) which should be prioritized for vaccination. The Prioritization Roadmap provides guidance on the epidemiological scenarios and outlines how these affect the prioritization of target populations. (2)

Initially, the evidence on vaccine use in specific populations will be limited by the populations included in the phase III trials. Nevertheless, based on these data, SAGE will consider whether the vaccine can and should be used in individuals for which there are no, or limited data as outlined above. Over time, as more data will become available, SAGE will consider further evidence, e.g. data generated from post-marketing studies.

In order to evaluate the vaccine characteristics for specific target populations as in the Prioritization Roadmap, these have been grouped based on underlying physiological and biological differences:

- Adults (≥18-59 years[2])
- Older adults (≥60 years[2])
- Individuals with comorbidities or health states that increase risk for severe COVID-19

As the evidence base evolves, SAGE will consider additional (refined) target populations (e.g., based on more disaggregated age cut-offs, children and adolescents, pregnant women, people living with HIV, and other).

Interventions

As a general principle across different antigens, SAGE aims to not issue product-specific recommendations but aims to encompass groups of products within its recommendations. Objective is to cover the large variety of products used in various settings worldwide. SAGE may only issue product-specific recommendations if there are compelling reasons (e.g., only one product is available).

For COVID-19 vaccines, analysis of data will be conducted on a product-by-product basis. Should the product-specific data then show comparable vaccine characteristics, recommendations will be grouped by vaccine platform (e.g. recommendations on the use of viral vector vaccines, on the use of nucleic acid vaccines, etc.).

[2] The age-thresholds were based on the WHO definitions. (9)

Comparisons

Comparison will be placebo or active control, as provided in current clinical trials. Future vaccines may have to be assessed on head-to-head comparisons, with no placebo group.

Outcomes

The key vaccine-specific outcomes are based on the principles and objectives as outlined in the Values Framework (Annex 4) and have been defined in the Compendium of critical questions. SAGE will consider data for all critical endpoints as listed in the Compendium, such as COVID-19 disease, severe COVID-19, transmission and serious adverse events, among other.

Questions to be considered in SAGE evidence-to-recommendation tables

Based on the PICOs and taking into consideration the initially limited clinical trial data, the SAGE will, in priority, initially issue evidence-to-recommendation tables for the following questions:

- Should COVID-19 vaccination be used in adults (≥18-59 years) to prevent COVID-19 disease?
- Should COVID-19 vaccination be used in older adults (≥60 years) to prevent COVID-19 disease?
- Should COVID-19 vaccination be used in individuals with comorbidities or health states that increase risk for severe COVID-19 to prevent COVID-19 disease?

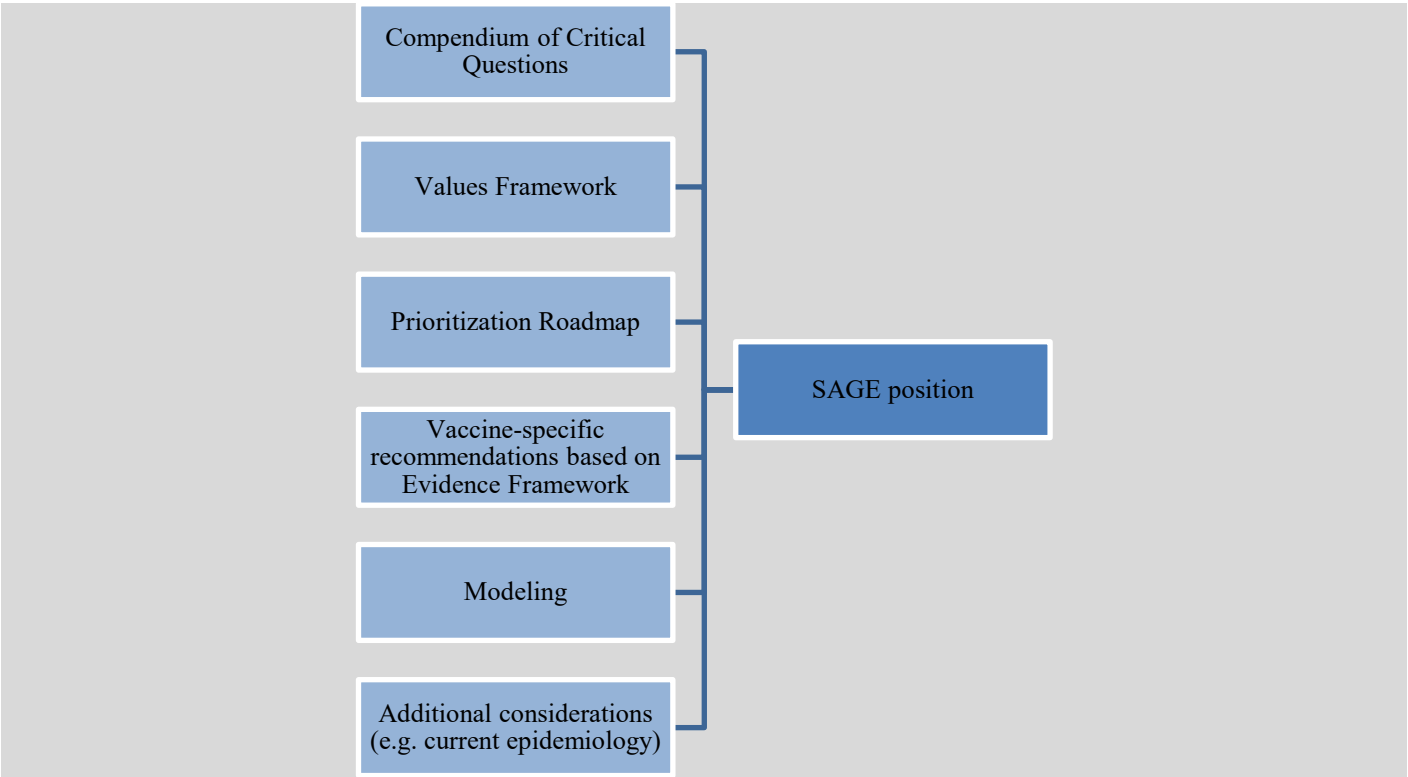
As the evidence base evolves, SAGE will consider issuing further evidence-to-recommendation tables as needed.

Moving to the proposed SAGE position

The SAGE position (recommendations proposed to WHO) will build on the Compendium, the Values Framework, the Prioritization Roadmap, the vaccine-specific recommendations, modeling efforts as well as additional elements, such as seropositivity and population seroprevalence levels, current disease epidemiology and implementation considerations. (Figure 1)

All these elements will be referenced and/or described in the SAGE Background Paper.

Figure 1: Process for developing the draft SAGE position.



Updating of the Evidence Framework

This Framework may be updated as needed, e.g., should additional evidence emerge.

Acknowledgments

This document was developed in consultation with the WHO SAGE Working Group on COVID-19 vaccines.

References

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Annexes

Annex 1: Prioritization of target populations for vaccination in a scenario of community transmission

Scenario: Community Transmission

Strategy: Initial focus on direct reduction of morbidity and mortality and maintenance of most critical essential services; also, reciprocity. Expand to reduction in transmission to further reduce disruption of social and economic functions.

Stage I (1-10%)	Stage II (11-20%)	Stage III (21-50%)
Stage Ia (initial launch) - Health workers at **high to very high risk** of acquiring and transmitting infection **Stage Ib** - Older adults defined by age-based risk specific to country/region	- Older adults not covered in Stage I - Individuals with comorbidities or health states determined to be at **significantly higher risk** of severe disease or death - Sociodemographic groups at **significantly higher risk** of severe disease or death - Health workers engaged in immunization delivery - High priority teachers and school staff	- Remaining teachers and school staff - Other essential workers outside health and education sectors - Pregnant Women - Health workers at **low to moderate risk** of acquiring and transmitting infection - Personnel needed for vaccine production and other high-risk laboratory staff - Social/employment groups at **elevated risk** of acquiring and transmitting infection because they are unable to effectively physically distance