

CRITICAL EVIDENCE QUESTIONS FOR COVID-19 VACCINES POLICY MAKING

STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE) ON
IMMUNIZATION WORKING GROUP ON COVID-19 VACCINES

PREAMBLE

This document lists areas of evidence that would assist SAGE to formulate policy recommendations for consideration by WHO regarding the use of COVID-19 vaccines as they become available. It is not intended as alternative to the lists of requirements for licensure as formulated by regulatory bodies nor does it replace or provide an alternative to the WHO Target Product Profile. Rather it reflects the evidence-needs for COVID-19 vaccine policy making, based on the current scientific thinking, to assist SAGE in deciding upon the optimal use given the limited vaccine supply in order to maximise impact on the pandemic in different populations and epidemiologic settings.

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1 BACKGROUND

The Strategic Advisory Group of Experts (SAGE) on Immunization is the principal advisory group to WHO for vaccines and immunization. SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations. SAGE Working Groups consider policy recommendations for vaccines based on the quality of evidence as outlined in its Evidence-to-Recommendation framework.¹

In June 2020, SAGE established a Working Group on COVID-19 vaccines. The Working Group will provide evidence-based information and options for recommendations for discussion by the full SAGE in an open forum. This Working Group will be requested to assist SAGE in advising WHO and its Member States on the accelerated use of vaccines (pre-licensure and post-licensure) to mitigate the public health impact of COVID-19, to possibly curtail the ongoing pandemic, as well as to prevent or reduce the risk of spread of disease in the future.. The timeliness of communicating data needs for policy decision-making will ensure a coordinated approach with the vaccine research and development (R&D) community, in order to accelerate timelines and maximize global efforts to make evidence-informed policy decisions for the best use of vaccines against COVID-19.

A [background paper](#) of relevant aspects related to COVID-19 vaccines has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines, and includes epidemiology, virology, immunology, clinical aspects, and vaccine-related aspects relevant for informing policy decisions regarding COVID-19 vaccines.

The “[WHO SAGE Values Framework for the Allocation and Prioritization of COVID-19 Vaccination](#)” lays out the overarching goal that COVID-19 vaccines must be a global public good. The overarching goal is for COVID-19 vaccines to contribute significantly to the equitable protection and promotion of human well-being among all people of the world. The framework further specifies the principles and objectives to provide a values foundation for WHO recommendations on priority target groups for COVID-19 vaccination programs at different stages of supply availability.

2 OBJECTIVE, SCOPE AND METHODS

The objective of this list of critical evidence questions is to enable SAGE to issue evidence-informed policy on the accelerated use of COVID-19 vaccines. The questions are grouped by criteria that SAGE takes into consideration in the context of vaccine policymaking and which are outlined in its Evidence-to-Recommendation framework¹:

- disease epidemiology and clinical profile;
- the benefits and harms of the options;

¹ GUIDANCE FOR THE DEVELOPMENT OF EVIDENCE-BASED VACCINATION- RELATED RECOMMENDATIONS. https://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf. Accessed August 2020

- values pertaining to the importance of the desirable and undesirable effects;
- equity and ethical considerations;
- feasibility and resource implications including economic considerations;
- social values and preferences, and acceptability;
- health-system opportunities and interaction with other existing intervention and control strategies.

One of SAGE's core principles is the transparency of its processes and decision-making. The quality of all data and literature will be assessed. For critical questions on vaccine immunogenicity/ efficacy/ effectiveness, duration of protection, and vaccine safety, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is WHO's standard for evidence-based decision-making, will be applied and will be reflected in the Evidence to Recommendation tables.

The document lists relevant questions on which evidence will be needed at different stages of decision making. The current list includes questions on which evidence will be needed in the earliest stages of decision making about whether to recommend use of a specific vaccine, and other questions for which evidence will only be available after vaccination – if recommended – would be implemented.

SAGE will issue recommendations to WHO on the use of those vaccines currently in the pipeline for which sufficient data are publicly available and which have obtained emergency use authorization or full licensure from a recognized regulatory body.

This following list of questions is not comprehensive, and with new evidence on COVID-19 emerging rapidly, evidence-needs are anticipated to shift or change from that captured below. SAGE may determine to issue recommendations even in the absence of evidence captured in the questions below.

3 PURPOSE

The purpose of this document is to guide SAGE and its Working Group in gathering the relevant evidence for decision-making along the criteria as set out in the SAGE evidence-to-recommendation table. The SAGE Working Group will use this list to reach out to respective groups within and outside of WHO to obtain information pertinent to the outlined questions. The list will also assist SAGE in identifying potential evidence gaps. Further, the intent of providing this high-level list of questions at this time is to help inform and orient researchers towards generation of the evidence that will be critical for SAGE recommendations at different stages of vaccine availability and vaccination implementation.

For all questions, evidence is sought across countries and epidemiological settings. This list of critical questions may assist country-level decision-making by highlighting the need to consider data beyond the safety and efficacy of a certain vaccine by taking into consideration key criteria such as acceptability, feasibility and ethical aspects, as outlined in the evidence-to-recommendation table.

4 EVIDENCE QUESTIONS

CRITERIA: PROBLEM STATEMENT

SARS-CoV-2 and COVID-19 Epidemiology

- I. What is the evidence on the breadth and magnitude of the burden of disease over time, including in different populations and epidemiologic settings?
- II. What is evidence on the epidemic trajectory with and without non-pharmaceutical and pharmaceutical interventions?
- III. What is the evidence that specific sub-populations are at increased risk of severe disease and death when infected?
 - Age groups
 - Sex
 - Individuals with specific co-morbidities
 - Individuals likely to be exposed to higher viral inoculum (e.g. health workers at high or very high risk of infection)
 - Specific subpopulations of equity concern (e.g. racial and ethnic groups, socially disadvantaged groups, vulnerable populations)
 - Pregnant and lactating women
- IV. What is the evidence that specific sub-populations are at increased risk of infection?
For example:
 - Frontline health workers and caregivers
 - Essential workers, where physical distancing is not feasible
 - Individuals in work or other settings, where physical distancing is not feasible
 - Individuals living in densely populated areas, including slums, prisons, and refugee settings
- V. What is the evidence that specific settings are associated with higher transmission?
For example:
 - Long term care facilities
 - Densely populated areas, including slums, refugee settings and prisons
 - Workplace where physical distancing is challenging or infeasible to implement
 - School or University settings
 - Congregate housing
 - Mass gatherings such as sport, cultural or other public events, religious gatherings and pilgrimages
 - Tourism and travel
- VI. What is the evidence on the demand for healthcare services, including the proportion of COVID-19 cases requiring health care at different levels of intensity (primary care/outpatient, secondary or tertiary care/inpatient, ICU, high-flow oxygen, ventilator) in different population subgroups (e.g. age groups) and geographic settings?

VII. What is the evidence on the long-term sequelae associated with COVID-19 disease, and, in infected persons, what is the evidence of the incidence and duration of long-term sequelae in different population subgroups (e.g. age groups) and geographic settings?

VIII. What is the evidence on the effects of specific treatment/clinical management options on reducing severe disease and mortality?

Indirect effects of COVID-19 pandemic

IX. What is the evidence of health-related indirect effects of the COVID-19 pandemic in different populations?

For example:

- Increased burden of disease of other health conditions, through disruption of health care services causing delay in diagnosis and treatment of other conditions (e.g. cancer and cardiovascular diseases)
- Decreased vaccine coverages
- Interruption of screening programs for health conditions
- Mental health (e.g. problems induced by lockdowns and physically distancing interventions)

Additional relevant questions

X. What is the evidence of economic and other societal effects of the COVID-19 pandemic, in different populations and population subgroups?

XI. What is the evidence of other indirect effects of the COVID-19 pandemic, such as restricted social contact and isolation, on different population groups?

For example:

- Educational attainment
- Poor access to food, malnutrition
- Child marriages
- Child abuse
- Domestic violence

CRITERIA: BENEFITS AND HARMS

WHO, within the protocol for the international randomised trial of candidate vaccines against COVID-19 ([Solidarity Trial](#)), suggests as a primary objective to evaluate the effect of each vaccine on the rate of virologically confirmed COVID-19, regardless of severity. Secondary and supportive endpoints include assessment of: efficacy against severe disease and death, duration of efficacy, efficacy by age or other subgroups, efficacy against SARS-CoV-2 infection, effect on transmission of SARS-CoV-2, and possible immunological markers as correlates of risk and/or protection.

SAGE suggests evidence for the above endpoints be evaluated as highlighted in the following questions.

I. Questions on direct effects

Clinical efficacy

- i) What is the evidence of an effect of immunization on efficacy against COVID-19 (regardless of severity); mild symptomatic, moderate, and severe disease; hospitalisations and death. How does efficacy vary by age-group (children, younger adults, older adults), by sex, in pregnant and lactating women, and in specific co-morbidity risk groups?
 - Measured as % vaccine efficacy and 95% confidence intervals
- ii) What is the evidence of an effect of immunization on efficacy against SARS-CoV-2 infection?
 - Measured as % vaccine efficacy and 95% confidence intervals
 - Measured difference in viral load (PCR Ct values) in upper respiratory tract samples
 - Measured as seroconversion to viral antigens not contained in the vaccine
- iii) What is the evidence of the efficacy of post-infection immunisation?

Immunogenicity

- i) What is the evidence of induction and levels of neutralising antibodies and of immunoassay-measured antibodies after partial or full primary vaccination in the different groups listed above (under clinical efficacy)?
 - Measured as concentrations/titres of antibodies or seroconversion rates vs pre-vaccination values or, if a correlate is established, seroprotection rates.
- ii) What is the evidence that immunobridging² can be used to estimate vaccine efficacy in specific groups for which clinical efficacy is not available from clinical trials? This is important as, based on the inclusion/exclusion criteria of the currently ongoing large phase III trials, certain population and age groups have in some instances been excluded from participation (e.g. infants, those with co-morbidities, pregnant and lactating women, etc.).

² Immunobridging is the conduct of an additional clinical trial in humans executed with the intent to extrapolate clinical human immunogenicity data to other populations of interest for use of a vaccine (e.g. certain age- or population groups) which were not included in the primary clinical trial.

- iii) What is the evidence of persistence of protective / neutralising / immunoassay-measured antibodies over time (over an interval lasting as long as feasible after completion of partial or full primary vaccination in the different groups listed above?)
- iv) For vaccines with regimens of two or more doses, what is the evidence for interchangeability of vaccines?

Effectiveness

- i) What is the evidence from observational post-implementation studies on vaccine effectiveness (in different populations)?
- ii) What is the evidence of effectiveness of the intervention in specific subpopulations?
- iii) What is the evidence of vaccine effectiveness after a single dose of vaccination/ after using an incomplete schedule?

Duration of protection

- i) What is the evidence of continued efficacy/ effectiveness of vaccination (in different populations)?

II. Questions on indirect effects and biomarkers

Transmission

- i) What is the evidence of the relation of viral shedding post-vaccination and SARS-CoV-2 transmissibility?
 - Measured as viral load among those infected
 - Other measures of infectiousness (e.g., subgenomic viral RNA)
- ii) What is the evidence of an effect of immunization on the duration of shedding of SARS-CoV-2?

Measured as viral shedding through active surveillance of respiratory tract sampling in vaccinated and control individuals
- iii) What is the evidence of reduction in new SARS-CoV-2 infections in contacts of vaccinated as compared to unvaccinated study subjects who become infected?

(For example: this could be answered by adjunctive protocols to large randomized controlled trials (RCTs), comparing infection rates among contacts of vaccinated and control study subjects)

- iv) What is the evidence of reduced rates of infection in unvaccinated individuals in vaccinated populations?

(For example: this could be answered by cluster randomised studies focussing on infection rates in un-immunised members of immunised clusters – if logistical and ethical challenges of undertaking such trials could be overcome)

Biomarkers and correlates of protection

- i) What is the evidence from functional antibody assays /neutralizing antibody assays? What is the evidence of their standardization and use in phase 1-3 clinical trials? What is the evidence that one or more of the described assays have been correlated to clinical protection?
- ii) What is the evidence from immunoassays used to assess responses to vaccines? What is the evidence that these assays have been correlated to functional/neutralization assays or to clinical protection?
- iii) What is the evidence concerning characterisation of T cell responses, both to naturally acquired infection and to vaccination that are (expected to be) protective?
- iv) What is the evidence that certain aspects of immune responses to vaccination (e.g. predominant development of certain types of CD4+ T cells, such as T helper cells (Th) type 1, over Th type 2 or Th type 17 and their distinct cytokine production patterns, elicited by the specific vaccine) are predictive of effective protection and/or absence of vaccine enhanced disease when exposed to SARS-CoV-2 following immunization?

Vaccine safety

- I. What is the evidence on rates of local and systemic reactogenicity signs and symptoms (e.g., pain at injection site, fever, headaches, malaise, etc.) using standardised definitions and ascertainment methods in the different target-populations and what is the impact on tolerability of the vaccine?
- II. What is the evidence of disease enhancement in either vaccine recipients subsequently exposed to the virus, in vaccine recipients with prior infection/pre-existing antibodies or those with incomplete immunization schedule?
- III. What is the evidence of any suspected unexpected serious adverse reactions (SUSARs), including but not limited to cases of (or absence of cases of) inflammatory disease or other manifestations following vaccination (e.g., mimicking pediatric multisystem inflammatory syndrome and toxic-shock - PIMS-TS)?
- IV. What is the evidence of adverse events of special interest (AESI), related or possibly related serious adverse events (SAE) and medically attended adverse events (MAAE) after vaccination (in all vaccinees with a minimum of 3 months, preferably up to 12 months, of follow-up after completion of administration of all doses in the vaccination schedule; in line with regulatory requirements and the points to consider for manufacturers of COVID-19 vaccines³)?
- V. What is the evidence of adverse maternal and neonatal outcomes after vaccination of pregnant women?
- VI. What is the evidence on co-administration of COVID-19 vaccines with other vaccines included in routine immunization schedule leading to decreased immune response to either vaccine?

³ [CONSIDERATIONS FOR EVALUATION OF COVID-19 VACCINES Points to consider for manufacturers of COVID-19 vaccines. www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf?ua=1](https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf?ua=1), accessed October 2020

- VII. What is the evidence that vaccinated persons are less likely to adopt other measures to reduce the risk of infection?

Metacriterion: Quality of the evidence

- I. What is the quality (GRADE) evidence of on vaccine efficacy/effectiveness, safety and duration of protection?

CRITERIA: VALUES AND PREFERENCES

Certainty of values and preferences

- I. What is the evidence of the certainty of the relative importance of the desirable and undesirable outcomes?
- II. What is the evidence of uncertainty or variability in the preference that target groups attribute to the harms and benefit outcomes?

Values and preferences of the target population

- I. What is the evidence of the target populations' value and preferences related to the intervention as well as the comparative health outcomes?
- II. What is the evidence that the benefits, harms, and costs of the intervention are valued differently by different populations (e.g. young vs old/ individuals with high vs. low socio-economic status)?

CRITERIA: RESOURCE USE

Economic burden of disease

- I. What is the evidence of the economic burden of disease, including direct medical, direct non-medical, and indirect costs (i.e., productivity losses) across all payers (e.g., government, private sector and non-governmental providers, patients and caregivers), and considering different perspectives (societal and health care system) without and with the intervention?

Resources to implement the intervention

- II. What is the evidence of the resources required to implement the intervention (costs of the immunization programme)?
- III. What is the evidence of the resources required to access the intervention from the beneficiary perspective (costs to the individual seeking and receiving vaccination and any caregivers of the vaccine recipient)?

Cost-effectiveness

- IV. What is the evidence of how cost-effectiveness of the intervention varies across different target populations and different settings, compared to no intervention?
- V. What is the evidence of how cost-effectiveness of the intervention compares with willingness to pay thresholds and cost-effectiveness of other recent interventions across settings?

- VI. What is the evidence of which parameters' uncertainty are most influential in estimating the cost-effectiveness of the intervention?

CRITERIA: EQUITY

Impact on health and social inequities

- I. What is the evidence of the impact of this intervention on health equity both between countries from different economic groups and within countries among wealth quintiles?
- II. What is the evidence on the impact of different prioritization vaccine strategies within countries on disease burden of COVID-19 by wealth quintiles and other relevant groups (e.g. ethnic, geographic, sex, etc)?
- III. What is the evidence that COVID-19 is more common in certain disadvantaged groups or is there evidence that the severity of COVID-19 is greater in people from specific groups or with a particular comorbidity?
- IV. What is the evidence of a risk that discrimination could impact outcomes?
- V. What is the evidence that significant differences in access could impact the vaccination coverage levels?

CRITERIA: ACCEPTABILITY

Acceptability to key stakeholders

- I. What is the evidence that the intervention is acceptable to stakeholders (ethically, financially, programmatically, financially, etc.)?
- II. What is the evidence of the acceptability to target group(s) to be vaccinated?
- III. What is the evidence of the acceptance of the intervention in above-mentioned population group(s)?

CRITERIA: FEASIBILITY

Feasibility of implementation

- I. What is the evidence that this intervention is accessible and acceptable to priority groups for vaccination (e.g. health workers, older adults, individuals with co-morbidities, etc.) and to providers?
- II. What is the evidence of the affordability of the intervention and how the resources required to implement the intervention compare to benchmarks of resource availability (e.g., historic budget levels, per capita spending levels, other vaccination interventions) in the same settings?

Provider feasibility

- I. What is the evidence that programmatic issues have been considered (e.g. costs related to health care worker's training and employment, logistic/cold-chain considerations), etc. to implement the intervention?
- II. What is the evidence of the requirements in terms of time, resources, and expertise to ensure adequate training, social mobilization, monitoring and supervision, supply chain logistics, cold chain storage, and supplies for safe and effective delivery of vaccines to prioritized populations?
- III. What is the evidence that the requirements are feasible and affordable to implement, for disadvantaged as well as advantaged populations?

Target population feasibility

- I. What is the evidence of the feasibility, affordability, and willingness to pay the direct and opportunity costs (e.g. additional visits to health care clinic) incurred by priority groups to implement the intervention?
- II. What is the evidence of demand for the intervention among priority groups?
- III. What is the evidence for which immunization delivery strategies are most likely to enable access by those in the priority population who wish to receive vaccination, considering values and preferences, resource use, and logistical factors?

CRITERIA: OTHER

Ethical considerations

- I. What is the evidence that proposed vaccine use recommendations are consistent with the 6 core principles as outlined in the "[WHO SAGE Values Framework for the Allocation and Prioritization of COVID-19 Vaccination](#)"?

Potential impact of vaccination strategies assessed by modelling

The SAGE Working Group on COVID-19 Vaccines previously issued a [Request for Information on prioritized infectious disease and economic modelling questions](#).

These prioritized modelling questions are provided below as a complete set for ease of reference with the previously issued document and its initial scenarios. These modelling questions are relevant additional critical questions under the criteria articulated in this document, including for benefits and harms of vaccine, resource use, equity, and feasibility.

a. Health and epidemiological impacts

- I. What is the evidence of what the impact of vaccinating each of the following target groups would be on SARS-CoV-2 infections, COVID-19 deaths, and COVID-19 years of life lost, for vaccines given during 2020-21 when vaccination is added to counterfactual scenarios of: (i) no interventions, or (ii) continued implementation of non-pharmaceutical interventions (NPIs)?
 - a. older adults (50+, 65+ or 75+ years)
 - b. younger adults (18-49 years)
 - c. school-age children (5-17 years)

- d. those at high risk of severe disease because of their underlying health conditions (e.g., cardiovascular disease, kidney disease)
- e. key workers (e.g., workers in health and social care, teachers)
- f. groups at high risk of infection (e.g., dense urban slums/informal settlements)

- II. What is the evidence for the optimal vaccination strategies in terms of target groups under different possible supply scenarios for COVID-19 vaccine during 2020-21 to achieve the maximum reduction in SARS-CoV-2 infections, COVID-19 deaths or years of life lost?
- III. What is the evidence of how health impacts would be distributed across country income groups (high, middle, low) and within countries across household wealth quintiles for the different vaccination targeting approaches described in Questions 1-2? (Note: distribution of impacts across other social groups is also of interest)
- b. Economic and social impacts
- IV. What is the evidence for the impact on protecting essential services (e.g., health and social care, education) of the different vaccination targeting approaches described in Questions 1-2?
- V. What is the evidence for the level of vaccine efficacy and vaccination coverage for which target groups could discontinue the use of NPIs that are most economically and societally disruptive (e.g., lockdowns, travel restrictions)?
- VI. What is the evidence for the impacts in terms of economic welfare (e.g., as measured by GDP growth) and economic security (e.g., as measured by number of people living in poverty) of different vaccination targeting approaches (e.g., those in Questions 1-2) across country income groups (high, middle, low)?
- VII. What is the evidence for what the cost-effectiveness per averted SARS-CoV-2 infection, COVID-19 death, and COVID-19 year of life lost would be, from the societal perspective, for the vaccination targeting approaches described in Questions 1-2?
- VIII. What is the evidence, in monetary terms, of what the full public health and societal value of vaccination is with a COVID-19 vaccine?

5 PLANS FOR UPDATING

SAGE and its working groups will continue to monitor the situation and may propose adjustments to these research questions if new evidence needs emerge.

6 ACKNOWLEDGMENTS

This document was developed in consultation with:

External: Current members of [SAGE](#) and the [SAGE COVID-19 Working Group](#).

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7 DECLARATION OF INTERESTS

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE and SAGE Working Group website.

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