How to better anticipate the desired effect of vaccines during outbreaks?

(What research data are needed to decide on optimal use of vaccines, beyond COVID-19?)

Alejandro Cravioto, M.D., Ph.D.
Facultad de Medicina, Universidad Nacional Autónoma de México,
Chair, Strategic Advisory Group of Experts (SAGE) on Immunization
World Health Organization
Geneva, August 29–30, 2022
Timelines for the malaria vaccine RTS,S (Mosquirix) from concept to the point of consideration for global policy recommendation

Malaria Vaccine Implementation Programme
Framework for Policy Decision

Mary J Hamel, IVR
SAGE
17 April 2018
Framework for Policy Decision for RTS,S

• MPAC and SAGE requested data be collected through the pilot implementations to answer questions on feasibility, safety, impact to inform a policy decision on wider use of RTS,S

• Framework for Policy Decision aims to describe how data will inform policy at the end of the pilots in 2022

• Also, will describe how data could inform
  1. Expansion of vaccinations into pilot comparator areas
  2. Broader country-wide implementation prior to 2022\(^1\) should emerging findings show:
     • Concerns about safety “resolved”
     • Implementation data “favorable”
     • Fourth dose coverage “high”

\(^1\) JTEG Background Paper on the RTS,S/AS01 Malaria Vaccine, Sep 2015
Context of COVID-19 response, and lessons learned to better prepare to respond to future pandemics

- Acceleration of the development and evaluation of candidate vaccines followed by expedited regulatory approval (e.g., US Food and Drug Administration (FDA) emergency use authorization (EUA), European Medicines Agency (EMA) conditional marketing authorization, WHO Emergency Use Listing Procedure (EUL)) and subsequent licensure
- Early deployment of scarce doses of vaccines (under accelerated review and approval) for priority populations required for public health benefits
- Limited data and evidence available to inform and support global policy decision-making
- Important to align the clinical trial and observational data or evidence anticipated to be needed for policy decisions for new vaccine for pandemics
- Enable planning for critical data collection along with the accelerated clinical trials to ensure rapid policy formulation and introduction of the new vaccines
Context for the need for evidence considerations for Vaccine Policy (ECVP)

Preferred Product Characteristics: (PPC):
defines product attributes for LMIC use

Scientific advice meetings:
Data on safety, quality and efficacy for licensure

WHO Policy & PreQualification

Proof-of-Efficacy

Proof-of-Effectiveness/Implementation

Financing & Procurement

Implementation

Sustainable supply

Licensure to policy and broad implementation

EVIDENCE CONSIDERATIONS FOR VACCINE POLICY:
evidence anticipated to facilitate global policy recommendations developed before phase III clinical studies

SAGE Evidence to Recommendation framework

WHO Position paper

Scientific advice meetings:
Data on safety, quality and efficacy for licensure

WHO PQ

What are these gaps in the existing guidance to navigate the end-to-end process?

<table>
<thead>
<tr>
<th>PPC parameters</th>
<th>WHO Policy Recommendation parameters</th>
<th>Gavi Vaccine Investment Strategy (VIS) parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB vaccines (adols &amp; adults)</strong></td>
<td>Recommendation(s) for use (Burden / recommended targeted risk population(s) by epi setting(s); other populations (permissive /contraindicated); geographies (regional, national, subnational), etc.)</td>
<td><strong>Health impact</strong>&lt;br&gt;Broader health system benefits</td>
</tr>
<tr>
<td>Indication for use, Target population</td>
<td>Benefits (pre-clinical and clinical; direct: effectiveness / preventable disease, and duration of protection; indirect: herd effect; etc.)</td>
<td><strong>Implementation feasibility</strong></td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Harm (pre-clinical and clinical; safety/ tolerability; benefit-harm-acceptance assessment; etc.)</td>
<td><strong>Vaccine cost</strong></td>
</tr>
<tr>
<td>Efficacy and proposed endpoints</td>
<td>Feasibility (implementation considerations: regimen, route, setting(s); storage, delivery, etc.)</td>
<td><strong>Value for money</strong></td>
</tr>
<tr>
<td>Durability of protection</td>
<td>Resource Use (Costs: illness; product &amp; implementation; Cost-effectiveness; Supply and wastage: vaccine &amp; delivery considerations; etc.)</td>
<td>Operational cost</td>
</tr>
<tr>
<td>Safety</td>
<td>Values &amp; Preferences (related to intervention &amp; comparative health outcomes)</td>
<td><strong>Equity &amp; social protection impact</strong></td>
</tr>
<tr>
<td>Dose schedule</td>
<td>Equities (Vaccine access; health, social, economic security, human rights/civil liberties, etc.)</td>
<td>Economic impact</td>
</tr>
<tr>
<td>Co-administration</td>
<td>Acceptability (by stakeholders; affordability, etc.)</td>
<td>Additional implementation costs</td>
</tr>
<tr>
<td>‘Dosage, regimen, and cost of goods should be amenable to affordable supply. Favorable cost-effectiveness should be established, and price should not be a barrier to access, including in low- and middle-income countries.’</td>
<td></td>
<td>Global health security impact</td>
</tr>
<tr>
<td>Source: WHO Preferred Product Characteristics for New Tuberculosis Vaccines</td>
<td></td>
<td>Gavi comparative advantage</td>
</tr>
<tr>
<td>Source: SAGE Guidelines development recommendations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Gavi Vaccine Investment Strategy

---

Efficacy and proposed endpoints

Feasibility (implementation considerations: regimen, route, setting(s); storage, delivery, etc.)

Resource Use (Costs: illness; product & implementation; Cost-effectiveness; Supply and wastage: vaccine & delivery considerations; etc.)

Values & Preferences (related to intervention & comparative health outcomes)

Equity (Vaccine access; health, social, economic security, human rights/civil liberties, etc.)

Acceptability (by stakeholders; affordability, etc.)
Strategic intent for Evidence Considerations for Vaccine Policy (ECVP) process and guidance

- Tool to facilitate **early and ongoing communication** between vaccine developers, regulators, policymakers, funders, public health authorities, researchers and technical experts at the national, regional and global level to **mutually outline** the anticipated data and evidence

- The ECVP should be available **before the design of pivotal licensure trials**, to be incorporated into trial designs and strategic vaccine development work planning

- For vaccine developers, **greater clarity on anticipated expectations for policy** will increase the likelihood that studies will meet requirements to generate optimal policies

- For new vaccines for priority diseases, the WHO ECVP aims to provide early information on the **clinical trial and observational data, or evidence** anticipated to be needed for WHO global, regional and country-level policy making, program decisions and program implementation

- Does **not preclude or supersede the independent SAGE** recommendations required for all vaccines seeking WHO policy recommendation. However, they will likely catalyse earlier formal discussions with SAGE on the anticipated evidence needs for future policy deliberations

- The ECVP will be **a living document** that is updated as new information becomes available; it will likely replace the WHO PPC and may serve as a helpful starting point for a vaccine specific SAGE WG.
Structure of the ECVP guidance

The ECVP is based on SAGE’s Evidence to Recommendation framework and includes six tables to describe the following parameters:

• Table 1: Vaccine Product Related Parameters
• Table 2: Regulatory Strategy Considerations for Initial Licensure
• Table 3: Vaccine Delivery related Parameters for the Priority Populations
• Table 4: Vaccination of Specific Populations
• Table 5: Implementation Considerations
• Table 6: Engagement and potential timelines or triggers

Each section identifies:

- **High Priority** parameters in red: expected to be critical for SAGE and other policy bodies at the regional and country level;

- **Medium Priority** parameters in blue: for which data and evidence are likely to be beneficial for policy recommendation.

➤ Prioritization of parameters can be adapted as needed
Vaccine related and delivery parameters included in the ECVP (red are critical; blue are beneficial)

Section 1: Vaccine related parameters
- Disease indication
- Priority target population/s
- Target countries
- Duration of protection at time of conditional approval and/or licensure
- Duration of protection (as part of effectiveness studies)
- Schedule (for primary series and booster)
- Route of administration
- Co-administration with other vaccines
- Measure of efficacy
- Efficacy endpoints in the clinical trial
  - Primary endpoints
  - Secondary endpoints
- Safety/reactogenicity
- Measure of Effectiveness
- Measure of efficacy/effectiveness against VOC/bacterial antigenic variation
- Measure of Immunogenicity

Section 3: Vaccine related parameters
- Vaccine delivery strategy/s for the primary target population
- Vaccine thermostability and storage temperature requirements
- Presentation
Section 5: Implementation related parameters included in the ECVP

• Provides information on the type of data that could inform policy, financing and introduction decisions by multiple actors, including policy-makers at the national, regional and global levels, as well as global financing agencies such as Gavi, civil society organisations and implementation partners.

• Intended to serve as a starting point to catalyse dialogue with regard to refining the data needs and expectations from different stakeholders depending on their specific contexts and policy scenarios.

• Several parameters will form part of the Gavi vaccine investment strategy (VIS) and likely needed for Gavi financing and initial policy introduction in Gavi-supported countries.

• Overarching activities related to implementation should include development of communication strategies to facilitate vaccine acceptability, build awareness, and generate demand. This requires generation of a robust communications and community engagement plan/program, vaccine-related events (VRE) response plan, and supporting materials which are updated throughout the development process.

• Issues and myths on the disease and vaccination need to be identified and addressed, prior to and during vaccination campaigns.
Section 5: Implementation related parameters included in the ECVP (red are critical; blue are beneficial)

- Feasibility (i.e., practicality of vaccine implementation, including in high burden countries (HBCs))
- Values and preferences of the target populations for vaccine (i.e., the likely acceptability of the vaccine)
- Demand potential (i.e., visibility into future uptake and market size, including for HBCs, that can inform market shaping discussions with stakeholders including donors, industry partners, and vaccine purchasers)
- Health Impact (i.e., the benefit of vaccination to the vaccinated individuals, and to the wider population)
- Economic impact (i.e., contribution of vaccine introduction to micro- and macro-economic benefits per country)
- Value for money (i.e., estimates on likely utility derived from budget spent in the target populations)
- Economic evaluation/Alternative interventions (i.e., Comparison of the cost and benefits, also relative to alternatives)
- Equity and social protection impact (i.e., prioritizing the needs and rights of the most vulnerable, and ensuring equitable benefit from vaccines)
- Access and affordability (i.e., ensuring that the vaccine will be made broadly and equitably available at an affordable price)
- Global health security impact (i.e., the potential benefit of the vaccine in averting bio-security risks)
Does the ECVP framework have applicability to better prepare for Pathogen X?

ECVP is a new tool that can:

➢ Enable planning for critical data collection along with the accelerated clinical trials to ensure rapid policy formulation and introduction of the new vaccines

➢ Facilitate early discussion/alignment on the clinical trial/observational data and evidence anticipated for policy decisions for new pandemic vaccines

A pathogen X ECVP would need to be developed by a WHO expert working group

- Generic ECVP framework developed and reviewed by SAGE; was published on the WHO website and can be adapted to different vaccines/diseases: https://www.who.int/publications/m/item/who-evidence-considerations-for-vaccine-policy-development-%28ecvp%29

- An exemplar ECVP for TB vaccines for adults and adolescents has been drafted by an expert WG, including RITAG chairs and SAGE members. Draft completed; public consultation will begin in September.
Acknowledgements – the WHO ECVP working group

- **WHO secretariat:** Birgitte Giersing & Dereck Tait (consultant)
- **ECVP working group chairs:** Sonali Kochhar & Helen Rees
- **ECVP working group members** (alphabetical order):
  - Marco Cavaleri – EMA
  - Huang Fei – China CDC
  - Mike Frick – Treatment Action Group
  - Gagandeep Kang – CMC Vellore/SEARO RITAG
  - Noni McDonald – Dalhousie University
  - Yalda Momeni – UNICEF
  - Andrew Pollard – University of Oxford
  - Richard White – LSHTM
  - Yauba Saidu – CHAI/ Cameroon NITAG

- **ECVP working groups observers** (alphabetical order):
  - Ann Ginsberg – BMGF (TB)
  - Ian Hudson – BMGF (DAC)
  - Shelley Malhotra – IAVI
  - Alexander Schmidt – GMRI
  - Marta Tufet/Cate Bennett – Gavi
  - Susan Wang – US CDC
  - Charlie Weller – Wellcome Trust

- SAGE Members and Secretariat