WHO activities to accelerate TB vaccine development and use

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Dept of Immunizations, Vaccines and Biologicals

4th April 2023
Global number of TB deaths increased in 2020 and again in 2021, back to 2017 level.

TB second only to COVID-19 as cause of death from single infectious agent.

- 1.6 million in 2021, up from 1.5 million in 2020 and 1.4 million in 2019.
- 187,000, down from 201,000 in 2020.
8 countries, 68% of global cases in 2021
87% in 30 high TB burden countries

China
Bangladesh
Philippines
India
Pakistan
Indonesia
Democratic Republic of the Congo

Number of incident cases
100,000
500,000
1,000,000
2,000,000
In 2014, WHO developed guidance on the preferred product characteristics for new vaccines to inform developers.

The WHO PPC document captures most key clinical and regulatory considerations for TB vaccines:

- Indication
- Target population
- Outcome measure; efficacy
- Duration of protection (at licensure; eventually)
- Safety
- Schedule
- Co-administration

Please see WHO vaccine PPC & Roadmap guidance documents under: Product Development for Vaccines Advisory Committee and PPCs.
One candidate, M72, has met the criteria of the WHO vaccine characteristics (and others are coming)

### VI. PPC FOR NEW TUBERCULOSIS VACCINES: USE IN ADOLESCENTS AND ADULTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td><strong>Immunization for prevention of active pulmonary TB disease.</strong></td>
<td></td>
</tr>
<tr>
<td>Target population</td>
<td>Adolescents and adults.</td>
<td>Adolescents and adults with TB disease represent the most common sources of Mtb spread and are therefore the WHO priority target for TB vaccine development. Demographic changes in some high endemicity countries justify inclusion of older adults in the target population. The optimal timing for paediatric evaluation should be discussed with regulators and policy makers but a paediatric clinical development program should certainly be considered when proof of concept is established in adolescents and adults.</td>
</tr>
<tr>
<td>Outcome measure and efficacy</td>
<td>50% or greater efficacy in preventing confirmed pulmonary TB.</td>
<td>A vaccine with lesser vaccine efficacy against confirmed TB in adolescents and adults, if widely used in areas of high TB endemicity, may still prove valuable and contribute to reducing the spread of Mtb in a cost-effective way (4), but this would fall short of the requirements necessary to meet the End TB goals by the 2035 target date.</td>
</tr>
<tr>
<td>Schedule</td>
<td>A minimal number of doses and boosters required.</td>
<td>A requirement for more than three doses to achieve primary immunization would not be desirable due to logistical and cost concerns.</td>
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</table>

- **M72/AS01E-4** met key criteria of the WHO PPC for adult/adolescent TB vaccines.
- The phase III efficacy study will begin in Q1 2024
Steps along the pathway to vaccine licensure— and use

**Regulatory approval:**
- Safety
- Quality
- Efficacy

**In countries**
- Feasibility,
- Acceptability,
- Cost effectiveness
- Cost benefit
- Self procuring countries could be early adopters

**Globally:**
- Data related to programmatic fit
- Data from sufficiently diverse and representative disease contexts
- ...and populations

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**Translational hurdle**

**Early to late stage dev’t**

**Discovery** — **Preclinical** — **Proof-of-Concept** — **Proof-of-Efficacy** — **Registration**

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**Translational hurdle**

**Early to late stage dev’t**

**Country introduction by policy makers and MoF**

**Discovery** — **Preclinical** — **Proof-of-Concept** — **Proof-of-Efficacy** — **Registration** — **Recommendation for use** — **Financing & Procurement** — **Implementation**

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**Translational hurdle**

**Early to late stage dev’t**

**Licensure to policy and broad implementation**

**Discovery** — **Preclinical** — **Proof-of-Concept** — **Proof-of-Efficacy** — **Registration** — **WHO policy & PreQualification** — **Proof-of-Effectiveness/Implementation** — **Financing & Procurement** — **Implementation**

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**Vaccine supply**
The data expectations for decision-making become more complex as a vaccine advances to policy, financing and introduction.

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<tr>
<td>Licensure to policy and broad implementation</td>
<td>Vaccine supply</td>
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### PPC Parameter
- Indication for use, Target population, Contraindications
- Efficacy
- Durability of protection
- Safety & Reactogenicity
- Dose regimen, Route of administration, Co-administration, Formulation/presentation, Product stability and storage
- Accessibility

### WHO Policy Recommendation parameter
- Recommendation(s) for use (Burden / recommended targeted risk population(s) by epi setting(s); other populations (permissive/contraindicated); geographies (regional, national, subnational), etc)
- Benefits (pre-clinical and clinical; direct effectiveness / preventable disease, and duration of protection; indirect herd effect; etc)
- Harm (pre-clinical and clinical; safety/ tolerability; benefit-harm-acceptance assessment; etc)
- 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)

### Gavi Vaccine Investment Strategy (VIS) Parameter
- Health impact
  - Broader health system benefits
- Implementation feasibility
- Vaccine cost
  - Value for money
  - Operational cost
  - Equity & social protection impact
  - Economic impact
  - Additional implementation costs
  - Global health security impact
  - Gavi comparative advantage

Source: [WHO TPP for COVID-19 vaccines](https://www.who.int/immunization/technical_guidance/training_modules/)  
Source: [SAGE: Guidelines development recommendations](https://www.who.int)  
Source: [Gavi Vaccine Investment Strategy](https://gavi.org)
Timelines for the malaria vaccine RTS,S (Mosquirix) from concept to the point of consideration for global policy recommendation

Alignment and co-ordination of stakeholders is crucial to achieving access and impact of new TB vaccines.
Extensive work on assessing the ‘full’ value of new TB vaccines by LSHTM and Harvard, under WHO framework

- Articulates the full value of new TB vaccines from the perspectives of multiple stakeholders

- Serves as an end-to-end compendium of available evidence to support advocacy and inform decision making at various stages of product development

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**Category** | **Needs**
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**Health gains** | Estimated potential impact of new TB vaccines on disease burden and transmission (including drug-resistant TB (DR-TB) and co-infection with HIV), as measured by incidence, mortality and morbidity (in the context of alternative strategies)

**Value for money** | Estimated societal cost-effectiveness/cost-utility and return on investment for new TB vaccines from the perspective of both the healthcare payer and society

**Equity and financial risk protection impact** | Estimated impact of a new TB vaccine on equity (in the context of health gains by income distribution and vulnerability) and reduced household financial vulnerability (catastrophic costs and impoverishment)

**Economic impact** | Estimated impact of new TB vaccines on medical and other expenses, as well as on gross domestic product and its rate of growth; estimated impact of new TB vaccines on government expenditure (including expenditure through the HIV response, as applicable) and on sustainability of financing over the long term

**Global health security impact** | An estimated impact of a new TB vaccine on antimicrobial stewardship (reducing antibiotic use, mitigating the reduced effectiveness of antimicrobials from continued use, reducing DR-TB disease incidence, reducing human and programmatic costs of DR-TB management, and improving health outcomes)

**Market** | Estimated potential demand for new TB vaccines

**Vaccine characteristics and implementation scenario assumptions** | The various parameters above should be evaluated under different vaccine characteristics and implementation scenario assumptions (target population, geographical scope and vaccine characteristics) In addition, the interaction between a new vaccine and alternative strategies (optimal use of current and future alternative interventions) on key outputs should be considered

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https://www.who.int/publications/i/item/9789240064690
WHO convened a series of workshops in 2021-22 to map what is needed.
WHO convened a series of workshops in 2021-22 to map what is needed.
Key variables to consider for the development of M72/AS01E demand forecast scenarios

- **Country scope and pace of introduction**
  - Which countries will introduce the vaccine?
  - For countries electing to introduce, what will be the year of introduction?

- **Scope of vaccination (national/subnational)**
  - Will introduction be done at a national or subnational scale?
  - Will all populations be targeted or only risk groups?

- **Booster dose requirements**
  - Will booster doses be required?
  - What is the frequency of boosters? Which populations are eligible?

- **Availability of vaccine supply**
  - How much vaccine supply will be available?
  - How quickly will supply reach maximum volumes?

**Vaccination coverage**

- Vaccination coverage is a key variable, if anticipated to vary significantly (e.g., 10-80%)
- This forecast is aimed at understanding influence of other key programmatic variables that could cause large variance in demand, assuming narrower ranges in vaccination coverage

Slide courtesy of MMGH
WHO convened a series of workshops in 2021–22 to map what is needed.
WHO is attempting to articulate the needs for global policy recommendations NOW, so that that data and evidence can be generated.

<table>
<thead>
<tr>
<th>PPC Parameter</th>
<th>WHO Policy Recommendation parameter</th>
<th>Gavi Vaccine Investment Strategy (VIS) Parameter</th>
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</table>
| Indication for use, Target population, Contraindications | Recommendation(s) for use (Burden / recommended targeted risk population(s) by epi setting(s); other populations (permissive/contraindicated); geographies (regional, national, subnational), etc) | Health impact
Broader health system benefits |
| Efficacy | Benefits (pre-clinical and clinical; direct effectiveness / preventable disease, and duration of protection; indirect: herd effect; etc) | Implementation feasibility |
| Durability of protection | Harm (pre-clinical and clinical; safety/ tolerability; benefit-harm-acceptance assessment; etc) | Vaccine cost
Value for money
Operational cost |
| Safety & reactogenicity | Feasibility (implementation considerations: regimen, route, setting(s); storage, delivery, etc.) | Equity & social protection impact
Economic impact |
| Dose regimen, Route of administration, Co-administration, Formulation/presentation Product stability and storage | Resource Use (Costs: illness; product & implementation; Cost-effectiveness, Supply and wastage: vaccine & delivery considerations; etc.) | Additional implementation costs
Global health security impact
Gavi comparative advantage |
| Accessibility | 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) | |

Source: [WHO TPP for COVID-19 vaccines](https://www.who.int/tpp)
Source: [SAGE Guidelines development recommendations](https://www.who.int/csr/disease/covid-19/sage)
Source: [Gavi Vaccine Investment Strategy](https://www.gavi.org/)

Immunization, Vaccines and Biologicals
Structure of the ECVP guidance

The ECVP is based on SAGE’s **Evidence to Recommendation** framework and includes five tables:

- Table 1: Vaccine Product Related Parameters for priority populations
- Table 2: Vaccine Delivery related Parameters for the priority populations, including delivery strategy/setting
- Table 3: Vaccination of other target populations (clinical and delivery considerations)
- Table 4: Regulatory Strategy Considerations to facilitate policy review
- Table 5: Implementation Considerations (data for decision making e.g. used in Gavi VIS)

Tables 1, 2 and 3 identify evidence needs for **initial (IP) and expanded (EP) policy** recommendations.

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.
Where are we now, with the ECVP tool and the TB vaccine ECVP?

Generic ECVP framework is available on IVB website

ECVP for TB vaccines intended for adults and adolescent vaccines has been through public consultation and is being finalized.
Initial policy considerations outlined in ECVP for TB vaccines for adults and adolescents

- Data demonstrating prevention of pulmonary TB disease as the primary endpoint, to ensure the most rapid impact on the TB epidemic due by reducing transmission.
- Data demonstrating safety and 50% or greater efficacy in preventing confirmed pulmonary TB
- **Efficacy data in adults with evidence of prior Mtb infection**
- **Safety and immunogenicity data** in adults without evidence of prior Mtb infection, to avoid the need for screening prior to vaccination.
- Safety and immunogenicity data from people living with HIV.
- Efficacy data from sufficiently diverse representative geographies to support global policymaking.
- A safety and reactogenicity profile supportive of widespread use of a preventive vaccine.
- Data demonstrating duration of protection for the disease indication of at least 2 years.
- Dosing regimens, schedule and delivery strategy designed for optimal cost-effectiveness and to achieve equitable impact, integrated within primary healthcare delivery systems
- Data relating to end-user acceptability, based on community engagement to ensure vaccine acceptance.
WHO convened a series of workshops in 2021-22 to map what is needed
WHO developing a global framework for country introduction of new adolescent and adult TB vaccines

<table>
<thead>
<tr>
<th>Vision &amp; Purpose</th>
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<tbody>
<tr>
<td><strong>A world free of TB, with zero deaths, disease, and suffering due to TB</strong></td>
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<table>
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<tr>
<th>Goals</th>
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<tbody>
<tr>
<td><strong>Facilitate rapid introduction and scale up of new adult and adolescent TB vaccines</strong></td>
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</table>

**Available**

- Sufficient, sustainable, and timely supply
  - Demand assessed (for short, medium and long term for priority populations; with regard to other interventions)
  - Policy, evidence needs, and pathways defined (e.g., approvals, recommendations, efficacy, and safety data required, specific populations; country testing)
  - Procurement plans in place (e.g., agreements with local and global manufactures, including on price, quantity and timing)

**Accessible**

- Equitable delivery aimed at all who could benefit
  - Implementation strategy defined (for priority populations; vis-à-vis interaction between primary health care, TB, HIV, school health, EPI programs; private providers)
  - Delivery systems in place (capacity; infrastructure; supply chains; pharmacovigilance; vaccine efficacy; phase IV studies)
  - Sustainable financing strategy in place (e.g., national health sector strategy, the Global Fund, Gavi, private pay)

**Accepted**

- Policymakers, end-users and health system requirements met
  - Value defined (i.e., at individual and population levels and from perspective of health workers, policy makers, vaccinees; vis-à-vis safety and efficacy)
  - Community engaged (i.e., priority populations, TB survivors, health workers, advocates, policymakers)
  - Robust communications strategy in place (e.g., localized; responsive to community concerns and priorities)

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**Programmatic suitability**

- Appropriate presentations
- Funded implementation research

**Regulatory and Policy**

- Appropriate phase III efficacy trials
- Rapid, harmonized regulatory pathways
- Licensure in high-burden countries
- WHO guidance/recommendation
- WHO prequalification

**Supply and manufacturing**

- Affordable vaccines
- Sufficient supply
- Sufficient and diversified manufacturing capacity
- Access, IP and procurement agreements

**Financing and political engagement**

- High level political will (G20/G7)
- Adequate financing
- Clarity on roles of funding partners (e.g., Gavi, the Global Fund) and procurement partners (e.g., PAHO, UNICEF)
Some activities under the different goals are related and should be tackled collectively

<table>
<thead>
<tr>
<th>Available</th>
<th>Accessible</th>
<th>Accepted</th>
<th>Timeframe (Short, Medium)</th>
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<tbody>
<tr>
<td><strong>Robust vaccine estimates for country demand</strong></td>
<td></td>
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<tr>
<td>Country-level modelling of demand</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Evaluate vaccine health and economic impact</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Engage TB programs and other national stakeholders to develop a robust demand forecast</td>
<td>✓</td>
<td>✓</td>
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<tbody>
<tr>
<td><strong>National policy pathway defined, and evidence gaps identified</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Define milestones/criteria for data and evidence requirements to inform policy decisions</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gather evidence needs for policy in parallel with clinical development for inclusion in regulatory dossier, streamline processes for rapid approval</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Conduct pre-implementation research</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td><strong>Procurement plans in place</strong></td>
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<td></td>
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<tr>
<td>Facilitate dialogue between manufacturers, regulators, and procurement partners</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Secure pricing and volume commitments from manufacturers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Assess the role of local and regional manufacturers</td>
<td>✓</td>
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</table>
WHO developing a global framework for country introduction of new adolescent and adult TB vaccines

Public consultation of Framework for country introduction of TB vaccines for adults and adolescents is ongoing:
https://www.who.int/publications/m/item/a-global-framework-to-prepare-for-country-introduction-of-new-tb-vaccines-for-adults-and-adolescents

<table>
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| • Appropriate presentations  
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• Sufficient supply  
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• Access, IP and procurement agreements | • High level political will (G20/G7)  
• Adequate financing  
• Clarity on roles of funding partners (e.g., Gavi, the Global Fund) and procurement partners (e.g., PAHO, UNICEF) |
UN high-level meeting on TB, 2023

**LEADERSHIP:**
OFFICE OF THE PRESIDENT OF THE GENERAL ASSEMBLY
with UNSG and WHO
H.E. Mr Csaba Kőrösi, President of the UN General Assembly

**Date:** 22 September, 2023
**Where:** UN Headquarters, New York

**Co-facilitators:**
Uzbekistan and Poland

**HLM outcome:** concise and action-oriented political declaration, agreed in advance by consensus through intergovernmental negotiations

**CIVIL SOCIETY HEARING:** 8-9 May, 2023

**Participants:**
UN Member States at the highest possible level, preferably at the level of Heads of State and Government; observers of the General Assembly; NGOs, civil society organizations, academic institutions and the private sector
WHO announces plans to establish a TB Vaccine Accelerator Council

17 January | Davos - The adverse impact of the COVID-19 pandemic on tuberculosis (TB) services has brought the urgency of vaccine development efforts into sharp focus. Speaking earlier today at a high-level panel on TB at the World Economic Forum, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization, announced plans to establish a new TB Vaccine Accelerator Council.

The Council will facilitate the licensing and use of effective novel TB vaccines catalysing high-level alignment between funders, global agencies, governments and end users in identifying and overcoming barriers to TB vaccine development.

“One of the most important lessons from the response to the COVID-19 pandemic is
Acknowledgements – many!

- **ECVP working group members** (alphabetical order):
  - ECVP working group chairs: Sonali Kochhar & Helen Rees
  - Marco Cavalieri – 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

Observers:
- 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
- Matteo Zignol, Nebiat Gebresselassie (WHO GTB)
- Sparks Street Advisors

**Country Introduction Framework WG members:**
- Babik Javid – UCSF
- Bader Al Ruwahi – Ministry of Health, Oman
- Carlos Martin – Universidad de Zaragoza
- David Lewinsohn – OHSU Center for Global Child Health Research
- Gagandeep Kang – CMC, Vellore
- Gerald Voss – TBVI
- Jimmy Galarza –
- Kawser Choudhury – SEARO RITAG
- Muluken Melese Aseresa – MSH
- Patrick Agbassi – Village Reach
- Peter Smith – LSHTM
- Puck Pelzer – KNVC
- Richard White – LSHTM
- Shelly Malhotra – IAVI
- Yanfeng Lim – CHAI
- MMGH consulting