Advances in new TB vaccine development and preparing for success

WHO PDVAC meeting
13th December 2023
Global TB control is suboptimal and will remain so without effective vaccines*

*Compared with drug, diagnostics and other advances, vaccines will have the largest impact
TB control has not fully recovered from Covid-19 setbacks

Number of people that developed TB disease*

Deaths

*410,000 had multidrug-resistant or rifampicin resistant TB
*TB vaccines efforts should include PLWHIV

WHO. Global TB Report. 2023
Where TB is common, or, where TB vaccines are needed

WHO. Global TB Report. 2023
TB incidence in 2022, relevant for efficacy trials

WHO. Global TB Report. 2023
**TB by age and sex, relevant for vaccine target populations**

Compared with case notifications (female in purple; male in orange), 2022

The highest burden is in men ≥15 years old - 5.8 million (55% of total)

Women aged ≥15 years - 3.5 million (33%)

Children 0-14 years old - 1.3 million (12%)

*Children do not spread TB while adolescents and adults do
*Targeting adolescent and adults to prevent TB disease will have earliest and largest impact
Overview of this session

1. Overview of the TB vaccine pipeline – Prof. Mark Hatherill (SATVI)

2. WHO activities to accelerate vaccine development and prepare for uptake – Dr Birgitte Giersing WHO – new TB vaccines lead

3. Analysis of potential outcomes of clinical studies and implications on regulatory and policy strategies – Dr Velislava Petrova (WHO consultant)
Does PDVAC consider the proposed/preliminary clinical and policy scenario framework to be useful to guide priorities for new TB vaccine development and readiness, and to identify gaps?

- If yes, what other components should be considered?
- How should such a framework be validated and used?
- Would there be value in publishing such a framework as a peer reviewed document?
The Tuberculosis Vaccine Pipeline

Strengths, Weaknesses, Opportunities & Threats

Mark Hatherill
South African Tuberculosis Vaccine Initiative (SATVI)
University of Cape Town
TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 16 vaccine candidates in the pipeline as of September 2023, of which 11 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

<table>
<thead>
<tr>
<th>Platform</th>
<th>Trial status</th>
<th>Candidate</th>
<th>Primary candidate indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterial - Live attenuated</td>
<td>Active trials</td>
<td>AdHuSAg8SA McMaster University, CanSino</td>
<td></td>
</tr>
<tr>
<td>Mycobacterial - inactivated</td>
<td></td>
<td>BNT164a1 BioNTech, Gates Foundation</td>
<td></td>
</tr>
<tr>
<td>Viral vector</td>
<td></td>
<td>BNT164a2 BioNTech, Gates Foundation</td>
<td></td>
</tr>
<tr>
<td>Protein/Adjuvant</td>
<td></td>
<td>ID93 + GLA-SE NIAID/NIH</td>
<td></td>
</tr>
<tr>
<td>DNA/RNA</td>
<td></td>
<td>DAR-901 Dartmouth</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>Prevention of infection</td>
<td>H56IC31 SSL, Valneva, JAVI</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Prevention of Disease</td>
<td>M72/AS01E Gates-MRI, GSK</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>Prevention of Recurrence</td>
<td>M72/AS01E Gates-MRI, GSK</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Therapeutic</td>
<td>RUT18 Archivel Farma</td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td>VPM1002 SiPL, VPM</td>
<td></td>
</tr>
<tr>
<td>mTB People without mTB infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+mTB People with mTB infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aTBd People with active TB disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR People with MDR-TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTB People cured of active TB</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Strength:** Diversity of vaccine platforms

**Weakness:** Few candidates (14 + BCG)

*BCG appears twice in the pipeline to distinguish between the investigation of its use in BCG-naive individuals (traveler vaccination) and in individuals who have previously been vaccinated with BCG (revaccination).*
Entering large Phase 3 licensure trial (Q1 2024): Results expected 2028
26,000 adolescents and adults aged 15-44 years, IGRA+(-); HIV-(+)

Efficacy, safety, and immunogenicity
- Safety & immunogenicity adolescents, adults, PLWHIV, IGRA+/-
- VE prevention of sustained IGRA conversion (IGRA-)
- VE prevention of TB disease (IGRA+)

Modelling projections M72/AS01E 50% VE
- Could prevent up to 76 Million TB cases and 8.5 Million TB deaths (25 years)
  - If VE in IGRA+ and IGRA-
TB Vaccine Pipeline

Active clinical trials of TB vaccine candidates

There are 14 active clinical trials across 12 candidates as of September 2023.

Platform
- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant
- DNA/RNA

Trial target population
- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- People without mTB infection
- People with mTB infection
- People with active TB infection
- People with MDR-TB
- People cured of active TB

Primary endpoint
- Sf: Safety
- POI: Prevention of Infection
- POD: Prevention of Disease
- POR: Prevention of Recurrence
- ThP: Therapeutic

Weaknesses:
- Few candidates in active trials (9 + BCG)
- Few candidates in Phase 1-2 (BNT164a/b1)
- Non-traditional efficacy trials (POI; POR; Tx; POD HHC)

Information reported by vaccine sponsors or found in clinical trial registries or other public sources.
For the full list of completed trials for each candidate, visit [www.newtbvaccines.org/tb-vaccine-pipeline/](http://www.newtbvaccines.org/tb-vaccine-pipeline/)

Last update: 28 September 2023
Opportunity:  Efficacy results positive (2023 - 2028) → 😊 funder/stakeholder sentiment, risk tolerance

BCG REVAX; VPM1002; RUTI; GamTBvac?

Threat:  Efficacy results negative (2023 - 2028) → ☹️ funder/stakeholder sentiment, risk aversion

BCG REVAX; VPM1002; RUTI; GamTBvac?

Weaknesses: Non-traditional efficacy trials

May not lead to global licensure

POD HHC  VPM1002
POR   H56:IC31; VPM1002
Tx    RUTI
POI  BCG REVAX; VPM1002
Way forward?
Opportunity: Efficacy results if positive (2023 - 2028): *M. vaccae* POD

Population-level health and economic impacts of introducing *Vaccae* vaccination in China: a modelling study

**Anhui Zhifei Longcom**

N=10,000

Aged 15 – 65 years

TST 15mm+

6 doses *M. vaccae* vs placebo

Follow up 2 years

Study completion Nov 2017

<table>
<thead>
<tr>
<th>Case definition</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of incident cases</td>
<td>29</td>
<td>64</td>
</tr>
<tr>
<td>Person-yr follow-up</td>
<td>8,846.3</td>
<td>8,838.2</td>
</tr>
<tr>
<td>Rate per 100 person-yr (95% CI)</td>
<td>0.328 (0.228, 0.472)</td>
<td>0.724 (0.567, 0.925)</td>
</tr>
<tr>
<td>Vaccine efficacy (% [95% CI])</td>
<td>54.7 (29.8, 70.8)</td>
<td>49.9 (-17.0, 78.6)</td>
</tr>
</tbody>
</table>

- **Definite pulmonary TB disease**
- **Microbiological pulmonary TB disease**
- **Smear or culture-positive pulmonary TB disease**
- **Definite Xpert MTB/Rif positive pulmonary TB disease**
- **Clinical TB disease**

---

NCT01979900
Opportunity: Discover & validate immune correlates of vaccine-mediated protection

Positive efficacy signal from Phase 2b trials (POI - BCG REVAX and POD - M72/AS01ₐ)

Key questions:
Single correlate, or signature of multiple correlates?
Specific to vaccine, or generalizable to other candidates?
Generalizable to other populations?
Discriminatory performance sufficient to avoid efficacy trial?
Threat: Lack POD efficacy data IGRA- and pre-adolescents

→ Are POI candidates at a dead end?
→ Disconnect between value proposition vs deliverable data (IGRA-; pre-adolescents)

**TB disease incidence (placebo arm)**
- IGRA+ (18-25 yr)  800 per 100,000
- IGRA+  640 per 100,000
- IGRA-  220 per 100,000

→ Sample size Phase 2b POD in IGRA negative  ~ n=14,000
→ Sample size Phase 3 POD in IGRA negative  ~ n=80,000

**Might never validate POI findings in IGRA- POD trial**
**Might never validate IGRA+ POD findings in IGRA- POD trial**
Unpublished data
ClinicalTrials.gov NCT02933281

Immuno-bridging? CD4 T cell response is different in IGRA- and IGRA+
H56:IC31; MTBVAC; M72/AS01E; ID93+GLA-SE; MVA85A; BCG; H1:IC31

Threat: Lack POD efficacy data IGRA- and pre-adolescents

Unpublished data
ClinicalTrials.gov NCT02933281

Safety and immunogenicity of candidate vaccine M72/AS01e in adolescents in a TB setting

Adams René Richard1,*, Hermen Goelanker1,*, Werner Barry1.
Robert van de Mevent2, Cheryl1, Day3, Colin4, Philippe Marx3, Mark Haefeli5,9, Oprahh4, Willem Hulskes5,9, the Vacuna Study Group.

Unpublished data
ClinicalTrials.gov NCT02933281

Induction and Regulation of T-Cell Immunity by the Novel Tuberculosis Vaccine M72/AS01 in South African Adults

D., Selby1,*, Michelle Tomasini2, Herz9, M. Mazibuko9, Werner Barry1, Willem Hulskes5, and the Vacuna Study Group.

Safety and immunogenicity of the novel tuberculosis vaccine ID93 + GLA-SE in BCG-vaccinated healthy adults in South Africa: a randomised, double-blind, placebo-controlled phase 3 trial

H1:IC31 vaccination is safe and induces long-lived TIF-2+IL-2+CD4 T cell responses in M tuberculosis infected and uninfected adolescents: A randomized trial

Nalisa Muwonge1, Hermen Goelanker1,*, Benjakitra M. Kuppusamy1,2, Anekulpadawat Modeer1,2, Brovanee Edie1,*, Ranjan K. K Das1,*, Willem A. Barlow2, Simon E. Day2, Simon Stock2, Robert van de Mevent1,2, Hermen Goelanker1,*, Andrew Kapler2, and Helen M. Graham2,9, the VACUNA study group.
Threat: Lack POD efficacy data IGRA- and pre-adolescents

→ Disconnect between value proposition vs deliverable data (IGRA-; pre-adolescents)

Routine vaccination of 9-year-olds
Plus 1-time vaccination for ages 10+

Cost-effective in 73/105 LMIC
Cost-saving in 58/105 LMIC
Economic benefits $283-474 billion (2050)
Assumes 50% efficacy in IGRA- and IGRA+ per WHO PPC
No efficacy data for IGRA+/− 9 year-olds
Likely never will

Routine vaccination of 9-year-olds would prevent (2050)
8.8 million TB cases
1.1 million TB deaths

Plus 1-time vaccination for ages 10+
Would prevent (2050)
44 million TB cases
5 million TB deaths
Opportunities:

- Pending efficacy trials
  - M72/AS01E (Phase 3)
  - MTBVAC (Phase 2b)
  - QTP101 (Phase 2b)
  - ID93+GLA/SE (Tx/POR)

- Pending trials PLWH + ART
  - VPM1002 and BCG
  - MTBVAC and BCG

- Pending Phase 1 FIH trials
  - H107
  - CMV vector (VIR-2020)

Recharging of the TB vaccine pipeline
**STRENGTHS**
- Diversity of vaccine platforms
  - mRNA, viral vector, protein subunit, inactivated mycobacterial, live mycobacterial
- Lead candidate with efficacy signal (M72/AS01E)
  - Partially meets WHO PPC (IGRA+)

**WEAKNESSES**
- Few candidates (14 plus BCG)
- Few candidates in active trials (9 plus BCG)
- Few candidates in Phase 1-2 (BNT164a/b1)
- Non-traditional efficacy trials - global licensure?
- Lead candidate with efficacy signal (M72/AS01E)
  - Partially meets WHO PPC (IGRA-)

**OPPORTUNITIES**
- Pending efficacy results if positive (2023-2028)
- Immune correlates of vaccine-mediated protection
- Rationale selection of vaccine antigens
- Pending trials
  - Phase 2b-3 POD / POR efficacy
  - Safety & Immunogenicity PLWH
  - Phase 1 FIH

**THREATS**
- Pending efficacy results if negative (2023-2028)
- Lack POD efficacy data IGRA- and pre-adolescents
  - Are POI candidates at a dead end?
  - Disconnect between value proposition vs deliverable data (IGRA-; pre-adolescents)
Acknowledgments

Study participants and their communities
Investigators and study teams
Sponsors and funders
Collaborators
Advances in new TB vaccine development and preparing for success

WHO PDVAC meeting
13th December 2023
Tens of thousands of years after emergence of human TB, new lessons about the disease, relevant for vaccine development.
Global TB control is suboptimal and will remain so without effective vaccines*

*Compared with drug, diagnostics and other advances, vaccines will have the largest impact
TB control has not fully recovered from Covid-19 setbacks

Number of people that developed TB disease*

*410,000 had multidrug-resistant or rifampicin resistant TB
*TB vaccines efforts should include PLWHIV
Where TB is common, or, where TB vaccines are needed
TB incidence in 2022, relevant for efficacy trials

WHO. Global TB Report. 2023
TB by age and sex, relevant for vaccine target populations*
Compared with case notifications (female in purple; male in orange), 2022

The highest burden is in men ≥15 years old – 5.8 million (55% of total)

Women aged ≥15 years – 3.5 million (33%)

Children 0-14 years old – 1.3 million (12%)

*Children do not spread TB while adolescents and adults do
*Targeting adolescent and adults to prevent TB disease will have earliest and largest impact
Overview of this session

1. Overview of the TB vaccine pipeline – Prof. Mark Hatherill (SATVI)

2. WHO activities to accelerate vaccine development and prepare for uptake – Dr Birgitte Giersing WHO – new TB vaccines lead

3. Analysis of potential outcomes of clinical studies and implications on regulatory and policy strategies – Dr Velislava Petrova (WHO consultant)
Questions for PDVAC

Does PDVAC consider the proposed/preliminary clinical and policy scenario framework to be useful to guide priorities for new TB vaccine development and readiness, and to identify gaps?

- If yes, what other components should be considered?
- How should such a framework be validated and used?
- Would there be value in publishing such a framework as a peer reviewed document?
WHO-led initiatives to accelerate new TB vaccine development and prepare for successful implementation

Birgitte Giersing PhD
Team Lead, Vaccine Prioritization and Platforms & New TB vaccine lead, Department of Immunization, Vaccines & Biologicals (IVB).

1st Working meeting of the TB Vaccine Accelerator Council
28 and 29 November 2023
A catalytic time for new TB vaccine development

Source: Stop TB Partnership, [https://newtbvaccines.org/pipeline-sortable/](https://newtbvaccines.org/pipeline-sortable/)
To date, no identified vaccine-induced correlate(s) of protection in humans – but work ongoing

Human protective immune responses only partially understood

No reproducibly predictive animal model(s) or human challenge model established

Effects of HIV status, infection (IGRA/TST) status, age and geography on vaccine efficacy must be determined for each vaccine

Inadequate capacity for multiple, overlapping registration-quality efficacy trials

Source: Stop TB Partnership https://newtbvaccines.org/pipeline-sortable/
There are two pathways to recommendation and use:

**National** regulatory approval and implementation pathway:

- Discovery & preclinical
- Early clinical
- Clinical Proof-of-Concept
- Pivotal Efficacy study
- Registration
- National policy
- Procurement
- Introduction & Implementation
- Sustainable Supply
- Self-procuring countries

**Global** regulatory approval and implementation pathway:

- Discovery & preclinical
- Early clinical
- Clinical Proof-of-Concept
- Pivotal Efficacy study
- Registration
- Effectiveness/Pharmacovigilance
- WHO global policy & PreQual.
- Global/regional Financing
- Global/regional Procurement
- Countries seeking financial support / pooled procurement
What are (some of) the challenges ahead?

- Health systems for targeting adults and adolescents with vaccines are poorly developed; the vaccine may be delivered outside usual vaccination sites.
- Identifying the optimal delivery strategy; it is not feasible to assess PoD in young adolescents, and vaccinating young adolescents requires a long duration of protection to cover peak age of risk.
- Range of epidemiological & health system contexts (burden, awareness, vaccine acceptability/interest, health system strength, political will...)
- Currently operating in the hypothetical – lack of alignment on vaccine attribute ‘absolutes’ and use cases - creates challenges for demand generation and demand assessment.
- Mechanisms and clarity exist to establish what data needed for regulatory approval, but not for global or national policy recommendations.
- No established financing mechanism for procurement of TB vaccines, particularly in high burden, middle income countries.

Uncertainty for investment from manufacturers.
What is WHO doing to address these challenges?

Efficacy targets against prevention of disease

Modelled vaccine impact aligned with WHO PPCs
Modelling studies indicate that a **vaccine for adolescents and adults will have a greater, more immediate impact** than vaccine for infants.

<table>
<thead>
<tr>
<th>Over 2025–2050</th>
<th>Vaccine for adolescents and adults (50% efficacy in preventing disease)</th>
<th>Vaccine for infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB cases averted</td>
<td><strong>37.2 – 76.0 million</strong> cases</td>
<td>5.8–18.8 million cases</td>
</tr>
<tr>
<td>TB deaths averted</td>
<td><strong>4.6 – 8.5 million</strong> deaths</td>
<td>0.8–2.6 million</td>
</tr>
<tr>
<td>Fighting Antimicrobial resistance</td>
<td>Avert 21.9–42.3 million treatments, save <strong>US$ 3.2 billion</strong> in treatment costs</td>
<td>Avert 2.4–8.6 million treatments, save <strong>US$ 299 million</strong> in treatment costs</td>
</tr>
<tr>
<td>Highly cost effective in nearly all high TB burden countries</td>
<td>Yes- for US$ 1 invested, US$ 7 in health and economic benefits</td>
<td>Yes</td>
</tr>
<tr>
<td>Advance health equity by averting TB-related household expenditure</td>
<td><strong>US$ 36.6–41.5 billion</strong> in savings (including 66% of total costs averted for the poorest 40% of the population)</td>
<td><strong>US$ 5.3 – 6.5 billion</strong> in savings</td>
</tr>
<tr>
<td>Gains in GDP</td>
<td>US$ 1.6 (0.8–3.0) trillion</td>
<td>US$ 0.2 (0.1–0.4) trillion</td>
</tr>
<tr>
<td>Return on investment</td>
<td>US$ 372 (283–474) billion</td>
<td>US$ 68.6 (44.5–100) billion</td>
</tr>
<tr>
<td>Market for TB vaccines (population requiring vaccination)</td>
<td>4.64 – 5.18 billion</td>
<td>1.32–1.43 billion infants</td>
</tr>
</tbody>
</table>

Source: An investment case for new tuberculosis vaccines, https://www.who.int/publications/i/item/9789240064690
What is WHO doing to address these challenges?

Anticipates data and evidence for global policy and WHO prequalification to reduce the gap between regulatory approval and global policy.
Some key take-aways from developing the Evidence Considerations on Vaccine Policy

- Data demonstrating safety and **50% or greater efficacy in preventing confirmed pulmonary TB disease**;
- **Efficacy data in adults and adolescents with evidence of prior/recent Mtb infection**, since this population accounts for 90% of TB disease and adults represent the most common source of Mtb spread – from **diverse representative geographies and epidemiological settings**.
- **Safety and immunogenicity data in adults and adolescents without evidence of prior/recent Mtb infection**, to support immunobridging to potential surrogates or correlates of protection and avoid the need for screening prior to vaccination.
- **Safety and immunogenicity data in people living with HIV** to enable rapid recommendation for use in this priority population.
- Data from **populations that may not have been adequately represented in licensure studies but are important in certain contexts**
- Dosing regimens, schedules, and delivery strategies designed **for optimal cost-effectiveness and to achieve equitable impact**, where possible, integrated within delivery systems for other vaccines or non-immunization programmes.
- Data relating to **end-user acceptability**, based on community engagement to ensure vaccine acceptance.
What is WHO doing to address these challenges?

**Efficacy targets** against prevention of disease

**Modelled vaccine impact** aligned with WHO PPCs

Anticipates data and evidence for global policy and WHO prequalification to **reduce the gap between regulatory approval and global policy**

Looks at what data, evidence and activities are needed at the country level, to prepare for introduction decision making.
WHO global framework to prepare for country introd’n of new adolescent and adult TB vaccines

<table>
<thead>
<tr>
<th>Vision &amp; Purpose</th>
<th>Goals</th>
<th>Milestones</th>
<th>Approach</th>
<th>Enablers</th>
</tr>
</thead>
<tbody>
<tr>
<td>A world free of TB, with zero deaths, disease, and suffering due to TB</td>
<td>Facilitate rapid introduction and scale up of new adult and adolescent TB vaccines</td>
<td>Available: Sufficient, sustainable, and timely supply</td>
<td>Accelerated, Coordinated, Integrated, People-centred, Equity-driven, Evidence-based</td>
<td>Programmatic suitability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accessible: Equitable delivery aimed at all who could benefit</td>
<td></td>
<td>Regulatory and Policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accepted: Policy makers, end-users and health system requirements met</td>
<td></td>
<td>Supply and manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Financing and political engagement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Demand assessed (for short, medium and long term for priority populations, with regard to other interventions)</td>
<td>• Appropriate presentations</td>
<td>• High level political will (G20/37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Policy, evidence needs, and pathways defined (e.g., approvals, recommendations, efficacy, and safety data required, specific populations; country testing)</td>
<td>• Funded implementation research</td>
<td>• Adequate financing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Procurement plans in place (e.g., agreements with local and global manufactures, including on price, quantity and timing)</td>
<td>• Appropriate phase III efficacy trials</td>
<td>• Clarity on roles of funding partners (e.g., Gavi, the Global Fund) and procurement partners (e.g., PAHO, UNICEF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Implementation strategy defined (for priority populations; vis-à-vis interaction between primary health care, TB, HIV, school health, EPI programs; private providers)</td>
<td>• Rapid, harmonized regulatory pathways</td>
<td>• Affordable vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Delivery systems in place (capacity; infrastructure; supply chains; pharmacovigilance; vaccine efficacy; phase IV studies)</td>
<td>• Licensure in high-burden countries</td>
<td>• Sufficient supply</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sustainable financing strategy in place (e.g., national health sector strategy, the Global Fund, Gavi, private pay)</td>
<td>• WHO guidance/recommendation</td>
<td>• Sufficient and diversified manufacturing capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Value defined (i.e., at individual and population levels and from perspective of health workers, policy makers, vaccinees, vis-à-vis safety and efficacy)</td>
<td>• WHO prequalification</td>
<td>• Access, IP and procurement agreements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Community engaged (i.e., priority populations, TB survivors, health workers, advocates, policymakers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Robust communications strategy in place (e.g., localized, responsive to community concerns and priorities)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is WHO doing to facilitate new TB vaccine readiness?

WHO Evidence Considerations for Vaccine Policy Development for Tuberculosis Vaccines Intended for Adults and Adolescents

Contents
I. Concept and strategic intent .......................................................... 11
II. Tables .................................................................................. 21
  Table 1: Vaccine product-related parameters ........................................... 22
  Table 2: Delivery-related parameters ...................................................... 31
  Table 3 – Vaccination of other target populations .................................. 35
  Table 4: Regulatory strategy considerations for initial licensure to help facilitate policy review .......................................................... 42
  Table 5. Implementation considerations .................................................. 46

Efficacy targets against prevention of disease

Modelled vaccine impact aligned with WHO PPCs

Anticipates data and evidence for global policy and WHO prequalification to reduce the gap between regulatory approval and global policy

Looks at what data, evidence and activities are needed at the country level, to prepare for introduction decision making

Critical gap analysis completed to drive coordination & actions
WHO and partners used the country framework to identify priority gaps, regarding activities and stakeholders engaged.
Global co-ordination within & across work streams, and alignment on assumptions is essential
Many partners, established and new, have recently entered the TB vaccine landscape.
Aim: To refine TB vaccine market demand analyses based on a review of TB vaccine forecasting efforts to date

Meeting Objectives
1. Present multi-country/global TB vaccine market demand assessment efforts by MMGH, IAVI and CHAI, with a view to understanding methodology and assumptions, limitations and gaps in existing efforts.
2. Gather feedback and discuss evidence needs for demand estimation with key stakeholders (policy makers, implementers, funders, civil society) to inform forecast refinement

Feedback from meeting
• Strategies will differ by country, driven by epidemiology
• Current constraints posed by the lack of existing delivery pathways—there is an opportunity/imperative in lead up to launch to strengthen pathways
• Likely to start out initially targeting the highest risk populations if supply constrained but to move to broader/routine roll out working through delivery linkage points (e.g. schools/universities) to ensure broader impact
• Data on vaccine hesitancy, acceptability and feasibility among key populations based on TPP, and fit in the context of other interventions (e.g. long acting TPT) needed
• Pricing will be an important determinant of demand and should be factored in market projection efforts

Going forward: Additional stakeholder validation from a broader range of country-specific settings needed. Parallel investment in strengthening delivery pathways in the lead up to launch needed.
Global alignment and co-ordination of stakeholders will be key.

Aims to facilitate the development, testing, authorization, and use of new TB vaccines
We’ve begun some work to develop a scenarios framework to identify the opportunities and gaps in the current pipeline – PRELIMINARY

<table>
<thead>
<tr>
<th>Country Milestones</th>
<th>Available</th>
<th>Accessible</th>
<th>Accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define policy, evidence needs &amp; pathways</td>
<td>Help define vaccine implementation strategy</td>
<td>Articulate value of TB vaccine to community</td>
<td></td>
</tr>
<tr>
<td>Access, IP &amp; procurement plans &amp; manufacturing</td>
<td>Build delivery systems</td>
<td>Community &amp; politicians engaged</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ensure adequate, sustainable financing</td>
<td>Robust communications strategy in place</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Governance and coordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set vision &amp; build consensus</td>
</tr>
<tr>
<td>Build clarity on roles &amp; responsibilities</td>
</tr>
<tr>
<td>Coordinate ongoing activities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programmatic Suitability</td>
</tr>
<tr>
<td>Communicate appropriate characteristics</td>
</tr>
<tr>
<td>Coordinate implementation research/strategy</td>
</tr>
<tr>
<td>Regulatoy &amp; Policy</td>
</tr>
<tr>
<td>Complete phase III efficacy trials &amp; Phase IV trials</td>
</tr>
<tr>
<td>Support licensure in high burden countries</td>
</tr>
<tr>
<td>Support regulation, policy &amp; guidance</td>
</tr>
<tr>
<td>Supply &amp; Manufacturing</td>
</tr>
<tr>
<td>Ensure sufficient and diversified manufacturing capacity</td>
</tr>
<tr>
<td>Support access, IP &amp; procurement agreements</td>
</tr>
<tr>
<td>Secure sufficient &amp; affordable supply</td>
</tr>
<tr>
<td>Engagement &amp; Financing</td>
</tr>
<tr>
<td>Conduct global &amp; regional advocacy</td>
</tr>
<tr>
<td>Ensure adequate, sustainable financing</td>
</tr>
<tr>
<td>Build high-level political will</td>
</tr>
</tbody>
</table>
What is WHO doing to proactively prepare for new TB vaccine approval and introduction?

The ECVP guidance anticipates data and evidence for global policy and WHO prequalification to reduce the gap between regulatory approval and global policy.
Why map policy scenarios for new TB vaccines?
What do we need to build the path to TB vaccine introduction?

- Prioritise critical questions
- Highlight evidence gaps
- Identify risks and trade offs
- Develop possible use cases
- Proactively provide guidance
TB vaccine pipeline: vaccines targeted at adults and adolescents based on public info

**POI**
- BCG
- Ad585A
- TB-Flu05E

**POD**
- VPM1002
- MTBVAC
- M72/AS01E
- GamTBVac
- mRNA
- ID93+GLA-SE QPT101
- M. Vaccae

**POR**
- H56:IC31
- VPM1002
- ID93+GLA-SE QPT101

**Phase 3 or later**
- M72/AS01E
- VPM1002
- GamTBVac
- M. Vaccae

**>1 country**
- M72/AS01E

**1 country**
- GamTBVac
- VPM1002
- M. Vaccae

**HBC & LMIC**
- M72/AS01E

**IGRA+/- & PLWHIV**
- M72/AS01E

**Phase 2b* or earlier**
- MTBVAC*
- mRNA?*
- ID93+GLA-SE QPT101
- AEC/BC02

**>1 country**
- MTBVAC*?
- mRNA?*

**1 country**
- MTBVAC*
- mRNA?

**HBC & LMIC**
- MTBVAC*?
- mRNA?*

**IGRA+/- & PLWHIV**
- MTBVAC*?

**Criteria described in the PPC and/or ECVP; and candidates that could be licensed by 2030**

* May advance to be in phase 3 before 2030
**Reality Check: Policy data needs vs. likely clinical trial outcomes**

**Data needed for policy and recommendation for introduction**
- Vaccine efficacy (>50%) in IGRA+ve and IGRA-ve adolescents and adults
- Vaccine efficacy (>50%) in PLWHIV
- Vaccine safety in IGRA+ve/IGRA-ve and PLWHIV
- Good representation of young adolescents in trials to enable deployment through existing vaccination programmes, e.g. for HPV.
- Representative data from diverse populations at risk (rather than only in high incidence settings) to enable recommendation for broader use.

**Data likely to be generated in clinical trails**
- Efficacy data in IGRA+ve population only
- Approval in IGRA-ve likely based on immunobridging
- Efficacy in PLWHIV inferred from immunogenicity data
- Safety data should be available for IGRA+/- and PLWHIV
- Most trials generate efficacy data in older adolescents (>15) or adults; need an acceptable approach to deliver to this population or to age de-escalate for use in 9–14 years olds, to enable broad delivery.
- In some cases, efficacy estimates rely on testing in high incidence settings and in a single country.
Prospective Timeline 2023-2030: TB vaccines for adults/adolescents

**VPM1002/Immuvac**
- 2024: Start of Ph3 in 7 countries (5 in Africa, 2 in Asia)
- 2025: Ph3 results from India (IGRA -/- & PLWHIV-)
  - Does not meet PPC/ECVP
- 2026: IGRA+/HIV- & PLWHIV- for 7 countries
- 2027: Ph3 results from Russian Federation (IGRA -/- & PLWHIV-)
  - Does not meet PPC/ECVP
- 2029: Possible data to enable national-level approval in India
- 2030: Possible data to enable national-level approval in Russian Federation

**GamTBVac**
- 2024: Ph3 results from India (IGRA -/- & PLWHIV-)
- 2027: Possible data to enable national-level approval in Russia
- 2028: Possible data for global recommendation

**M72/AS01E**
- 2024: Start of Ph3 in 7 countries (5 in Africa, 2 in Asia)
- 2025: Completion of recruitment
- 2026: Interim analysis (IGHRA+/HIV-)
- 2027: Final analysis (IGHRA+/HIV-)
- 2028: End of follow up (IGHRA+ & PLWHIV for 7 countries)
- 2029: Possible data for national level approval in South Africa
- 2030: Possible data to enable national level approval in SA, even with Ph2b results

**MTBVAC**
- 2025: Start of Ph2b in South Africa
- 2026: Ph2b results for IGRA +/- & PLWHIV in South Africa
- 2029: Possible data for national level approval in South Africa
What do we begin to learn from preliminary mapping?

<table>
<thead>
<tr>
<th>Prioritise critical questions</th>
<th>Highlight evidence gaps</th>
<th>Identify risks and trade offs</th>
<th>Develop possible use cases</th>
<th>Proactively provide guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Timelines for data availability and degree of alignment with national and global policy needs</td>
<td>• Consensus on licensure path for 9–14-year-olds</td>
<td>• Choice of vaccine with different dosing schedules</td>
<td>• Introduction based on national vs. global recommendation</td>
<td>• Alignment with other vaccine programmes (routine vs. campaign vaccination)</td>
</tr>
<tr>
<td>• Country self-financing capacity and demand</td>
<td>• IGRA+ status of broader population in HBC</td>
<td>• Possible supply and demand misalignments</td>
<td>• Introduction in self-funded vs. Gavi-funded countries</td>
<td>• Degree of reliance/acceptability on inferred vs. direct measurement of efficacy in IGRA− &amp; PLWHIV</td>
</tr>
<tr>
<td></td>
<td>• Acceptability of different vaccine program options</td>
<td>• National and regional acceptability/pre-requisites, from a manufacturing and data perspective</td>
<td>• Introduced as part of immunization or TB Control programme?</td>
<td></td>
</tr>
</tbody>
</table>
Next steps

- Feedback on value and utility
- Prioritization of key questions and parameters
- Broader consultations and sharing of preliminary findings
- Publishing of the work?
Questions for PDVAC

Does PDVAC consider the proposed/preliminary clinical and policy scenario framework to be useful to guide priorities for new TB vaccine development and readiness, and to identify gaps?

- If yes, what other components should be considered?
- How should such a framework be validated and used?
- Would there be value in publishing such a framework as a peer reviewed document?