Global Vaccine and Immunization Research Forum Webinar
New Tuberculosis Vaccines for Adults and Adolescents: Progress, Prospects, and Perspectives
22nd February 2024
15.00 – 18.30 CET
Overview of the webinar

PART 1: BCG is not enough
PART 2: TB vaccines for adults and adolescents on the horizon
PART 3: Innovation and new tools in TB vaccine development
PART 4: Preparing for success

Panel discussions will consider:

- What are the major bottlenecks to TB vaccine development for this new population, and what is needed to de-risk investment?
- Do we have the tools needed to identify and down-select new TB vaccine targets?
- What are the priorities to prepare the pathway for new TB vaccine implementation, particularly for adults and adolescents?

Latest information and materials from past meetings are available at:

Questions? Please email gvirf@who.int

With support from

[Logos of NIH, Bill & Melinda Gates Foundation, World Health Organization, and TechNet-21]
Current status of the global TB epidemic

Nebiat Gebreselassie
Global TB Programme
TB affects every country of the world, but its magnitude & impact are greatest in low-and-middle income countries.

✓ Approximately 87% of global TB cases are in 30 high TB burden countries

✓ Eight countries accounted for 68% of global cases in 2022
TB REMAINS ONE OF THE TOP INFECTIOUS KILLERS IN THE WORLD

It is the leading cause of death of people with HIV and a major contributor of antimicrobial resistance related deaths.

In 2022,

• **1.3 million** people died from TB

• **10.6 million** people fell ill with TB

About a quarter of the global population is estimated to have been infected with TB bacteria.
TB more badly impacted than HIV

Deaths from TB in 2022 almost double those from HIV/AIDS, which continued to fall.

Shaded areas show 95% uncertainty intervals.
Distribution by age and sex

5.8 million men (55%), 3.5 million women (33%), 1.3 million children (12%)
Global recovery in reported number of people newly diagnosed with TB

7.5 million in 2022: highest number since WHO started global TB monitoring in mid-1990s

COVID-related disruptions resulted in about half a million excess deaths from TB in 2020, 2021, 2022
Estimated number of people developing MDR/RR-TB relatively stable from 2020–2022

- Two in five people with MDR/RR-TB did not access treatment
- 63% treatment success rate (latest cohort data)

Shaded area shows 95% uncertainty interval
GLOBAL ESTIMATES OF TB CASES ATTRIBUTABLE TO 5 RISK FACTORS IN 2022

- TB is driven by complex health and social determinants such as undernutrition and poverty.
- Approximately half of people who develop TB disease face significant financial hardship because of their illness.
Progress with respect to TB research and innovation

Status of clinical development pipeline for diagnostics, drugs and vaccines (August 2023)

- 3 new diagnostic products to detect drug-resistant TB recommended by WHO in 2023
- 16 vaccine candidates in clinical trials
- 28 drugs for treatment of TB disease in clinical trials
- 29+ clinical drug trials and other research studies for treatment of TB infection
Global tuberculosis targets - 2023 UNGA political declaration on TB

<table>
<thead>
<tr>
<th>Target</th>
<th>Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB treatment coverage</td>
<td>90% by 2027</td>
</tr>
<tr>
<td>Coverage of TB preventive treatment for priority groups (household contacts of people with TB; people living with HIV)</td>
<td>90% by 2027</td>
</tr>
<tr>
<td>Coverage of rapid diagnostic testing for TB</td>
<td>100% by 2027</td>
</tr>
<tr>
<td>Coverage of health and social benefits package for people with TB</td>
<td>100% by 2027</td>
</tr>
<tr>
<td>Development and availability of new TB vaccines that are safe and effective</td>
<td>Rollout initiated, preferably within 5 years</td>
</tr>
<tr>
<td>Annual funding for universal access to quality prevention, diagnosis, treatment and care for TB</td>
<td>US$ 22 billion by 2027, US$ 35 billion by 2030</td>
</tr>
<tr>
<td>Annual funding for TB research</td>
<td>US$ 5 billion by 2027</td>
</tr>
</tbody>
</table>
FOR MORE INFORMATION

THANK YOU!
The Investment Case for New TB vaccines

Richard White, Nick Menzies, Rebecca Clark, Allison Portnoy, Christina Mukandavire, Chathika Weerasuriya, Danny Scarponi, Arminder Deol, Andrew Iskauskas, Roel Bakker, Matthew Quaife, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, Raymond Hutubessy, Birgitte Giersing, Mark Jit, Rebecca Harris, So Yoon Sim, Inés Garcia Baena, Nobuyuki Nishikiori, Jean-Louis Arcand, Edith Patouillard,

and many, many others

richard.white@lshtm.ac.uk
Background

TB Vaccines

• Key to reaching WHO End TB goals
• WHO created preferred product characteristics (PPCs) for new infant and adolescent/adult vaccines
• Development expensive and long and licensure needs phase III field efficacy study (later today)
• Poorly known market size (later today) and ROI
• Lack of market incentives to invest

Objectives: Estimate the potential health, economic and wider impact in LMICs of vaccines meeting the technical specifications of the WHO PPCs
Apply Full Value of Vaccines Assessment (FVVA) Framework

- Lack of market incentives to invest
- Essential to address value beyond direct health impact
- Apply FVVA to capture broader economic and wider impacts
Health estimation methods

- TB infection transmission and economic model (TBVax)
- Model separately 105 low and middle income countries
- Captured 93% of TB incidence in LMICs
- Model forward to 2050 without no new vaccine introduction ("No-New-Vaccine" baseline)
- Compare to scenarios with a new vaccine modelled

Outcomes

- Cumulative cases, treatments & deaths averted
- Between year of vaccine introduction (varies) and 2050
- Countries grouped into
  - WHO region,
  - World Bank income group,
  - WHO high TB burden countries

\[ D_c = \text{Clinical Disease}, \quad D_s = \text{Subclinical Disease}; \quad I_f = \text{Infection-Fast}, \quad I_s = \text{Infection-Slow}; \]
\[ R = \text{Resolved}, \quad T = \text{On-Treatment}, \quad U_c = \text{Uninfected-Cleared}, \quad U_n = \text{Uninfected-Naive} \]
Informed by WHO Preferred Product Characteristics for New Tuberculosis Vaccines

<table>
<thead>
<tr>
<th>Vaccine Age Group</th>
<th>Infection status at time of vaccination required for vaccine efficacy</th>
<th>Prevents</th>
<th>Vaccine Efficacy</th>
<th>Duration of Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent / Adult</td>
<td>Pre and Post Infection with <em>Mtb</em></td>
<td>Disease</td>
<td>50% (75%)</td>
<td>10 years</td>
</tr>
</tbody>
</table>

Vaccine delivery methods

**Accelerated Scale-up**
- All countries introduce in 2025
- Instant scale-up to coverage
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+

**Basecase**
- Country-specific intro years
- Scale-up to coverage over 5 years
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+

**Routine Only**
- Country-specific intro years
- Scale-up to coverage over 5 years
- Adolescent/adult vaccine: routine 9-year-olds

**Basecase vaccine coverage after 5 years**
- Neonatal: 85%
- 9-year-olds: 80%
- 10+: 70%

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**Graphical Representation**

- **Self-procuring**
  - Coverage target reached instantaneously
  - Campaign target reached in Year 1

- **Gavi**
  - Routine scale up to target coverage
  - Country-specific introduction years

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<table>
<thead>
<tr>
<th>Year</th>
<th>2025</th>
<th>2026</th>
<th>2027</th>
<th>2028</th>
<th>2029</th>
<th>2030</th>
<th>2031</th>
</tr>
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<tbody>
<tr>
<td>Neonatal</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>9-year-olds</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>10+</td>
<td>0%</td>
<td>0%</td>
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An adolescent/adult TB vaccine may reduce incidence rates in 2050 by 25%

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

In line with previous LMIC modelling (Knight 2014)

• Important health impact
  → ~25% reduction in cases in 2050
Vaccination adolescent/adults may lead to greater & more rapid incidence rate reductions in 2050, than vaccinating infants vs Infant, 80% efficacy, Basecase delivery, 10y protect, med coverage

Greater impact from an adolescent / adult vaccine vs. infant vaccine before 2050

→ Targeting the age group with the largest burden
An adolescent/adult vaccine may avert ~44m cases, ~25m treatments, and ~5m deaths by 2050

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

Cumulative cases averted between vaccine introduction and 2050
- Potential to avert ~44 million cases
  - Particularly in AFR and SEAR

Cumulative treatments averted between vaccine introduction and 2050
- Potential to avert ~25 million treatments by 2050
  - Valuable contribution to averting antimicrobial resistance

Cumulative deaths averted between vaccine introduction and 2050
- Potential to avert ~5 million deaths by 2050
Introducing at rate of COVID-19 vaccination may avert \(~50-60\%\) more cases/deaths, than introducing at rate of other earlier vaccines

Adol/Adult, 50\% efficacy, varying delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by delivery:
We assumed more ‘realistic’ introduction & scale up scenarios than previous modelling

In the Basecase scenario, \(~44\text{ million}\) cases, \(~25\text{ million}\) treatments, and \(~5\text{ million}\) deaths were averted.

An increased scale-up speed (Accelerated Scale-up) could prevent \(~21\text{ million additional}\) cases, \(~14\text{ million additional}\) treatments, and \(~3\text{ million additional}\) deaths \((\sim 50-60\%\) more\)
Routine only delivery may avert ~80-90% fewer cases/deaths, than the routine & campaign

Adol/Adult, 50% efficacy, varying delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by delivery:
We assumed more ‘realistic’ introduction & scale up scenarios than previous modelling

In the Basecase scenario, ~44 million cases, ~25 million treatments, and ~5 million deaths were averted.

- An increased scale-up speed (Accelerated Scale-up) could prevent ~21 million additional cases, ~14 million additional treatments, and ~3 million additional deaths (~50–60% more)
- By only offering this new TB vaccine routinely to adolescents (Routine Only), ~35 million fewer cases, ~22 million fewer treatments, and ~4 million fewer deaths would be averted (~80-90% fewer)
A 75% efficacy vaccine may avert ~50% more cases/deaths, than a 50% efficacy vaccine

Cases, treatments, and deaths averted by Basecase delivery with 50% vs 75% efficacy and 10 years vs lifelong protection

In the Basecase scenario, ~44 million cases, ~25 million treatments, and ~5 million deaths were averted.

- A vaccine with 75% efficacy could prevent ~20 million additional cases, ~14 million additional treatments, and ~2 million additional deaths (~50% more)
Infant TB vaccines cost-effective in 45% of countries (89% high-burden countries)

- Higher country incidence rate associated with higher impact per capita, more favorable CE

Health system perspective

Diagonal line represents cost-effectiveness threshold of 1x per-capita GDP. Vaccine introduction is considered cost-effective for countries falling underneath this line.

Higher country incidence rate associated with higher impact per capita, more favorable CE

Same story for adult vaccine, but higher average costs and impact

Adol/Adult TB vaccines cost-effective in 61% of countries (100% high-burden countries)

TB vaccines may be cost-saving from societal perspective

$7 in health and economic benefits, for every $1 invested in adolescent/adult TB vaccines

Includes all LMICs for which vaccine introduction is cost-effective at a given willingness-to-pay threshold.
TB vaccines may advance health equity, with ~56% of benefits in poorest 40% of the population

Lower income quintiles:
- Higher TB incidence
- Greater proportion with catastrophic costs
Adol/Adult TB vaccines may increase LMIC GDP by $1.6 trillion by 2080

- Macroeconomic impact strongly related to current TB incidence level
- Earlier vaccine introduction, lower current GDP per capita also related to greater % impact

Summary

• Case for new adolescent/adult TB vaccines is strong

• Potentially impactful, reduce AMR, cost effective (even cost-saving), advance health equity, increase GDP

• Adol/adult vaccine likely quicker & larger impact than infant vaccine

• But really need for campaigns to get this impact, not just routine

• Need to include poor and other higher burden groups to maximize impact and advance equity
Needs

• Adol/adult vaccine(s) will (hopefully) be licensed, but will be for ~15–44 year olds

• Many key risk groups, and/or more operationally feasible groups, lie outside

• Will need rapid
  • Age de-escalation for younger adolescent
  • Age escalation for older groups

• Big gap between country level decision makers data needs and data availability
  • Eg 20 HBCs experts said >74% need potential vx impact data but only <24% have data
  • Need coordinated data collation, collection & generation needed

Clark et al, in review
Summary of...

Policy Brief

An investment case for new tuberculosis vaccines

Health Impact

The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study

Rebecca A. Clark, Christelike Mukandavire, Alison Portnoy, Chathika K. Weneerasu, Amanda Dye, Simon Spering, Andrea Manzi, Roy Aikins, Matthew Quirke, Shefy Mathane, Nebert Gebreabedis, Matteo Ziglio, Raymond OF McIntosh, Bryan Gerring, Mark Jh, Rebecca Danchi, Nicolas A. Membes, Richard G. White

Summary

Background Tuberculosis is a leading infectious cause of death worldwide. Novel vaccines will be required to reach global targets and reverse setbacks resulting from the COVID-19 pandemic. We estimated the impact of new tuberculosis vaccines in low-income and middle-income countries (LMICs) in several delivery scenarios.

Cost and cost effectiveness

The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: A modeling study

Alison Portnoy,*, Rebecca A. Clark,*, Matthew Quirke,*, Chathika K. Weneerasu,*, Christelike Mukandavire,*, Roy Aikins,*, Amanda Dye,*, Shefy Mathane,*, Nebert Gebreabedis,*, Matteo Ziglio,*, So Yoon Shin,*, Raymond OF McIntosh,*, Bryan Gerring,*, Mark Jh,*, Rebecca Danchi,*, Nicolas A. Membes,*, Richard G. White,*, Nicola A. Membes

Equity and financial protection

The potential impact of novel tuberculosis vaccines on health equity and financial protection in low-income and middle-income countries

Alison Portnoy,*, Rebecca A. Clark,*, Chathika K. Weneerasu,*, Christelike Mukandavire,*, Matthew Quirke,*, Roy Aikins,*, Shefy Mathane,*, Nebert Gebreabedis,*, Matteo Ziglio,*, Mark Jh,*, Richard G. White,*, Nicolas A. Membes

Macroeconomic growth

The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries: A modeling study

Alison Portnoy,*, Jean-Louis Arsenault,*, Rebecca A. Clark,*, Chathika K. Weneerasu,*, Christelike Mukandavire,*, Roy Aikins,*, Shefy Mathane,*, Nebert Gebreabedis,*, Matteo Ziglio,*, Mark Jh,*, Richard G. White,*, Nicolas A. Membes
The Investment Case for New TB vaccines

Richard White, Nick Menzies, Rebecca Clark, Allison Portnoy, Christinah Mukandavire, Chathika Weerasuriya, Danny Scarponi, Arminder Deol, Andrew Iskauskas, Roel Bakker, Matthew Quaife, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, Raymond Hutubessy, Birgitte Giersing, Mark Jit, Rebecca Harris, So Yoon Sim, Inés Garcia Baena, Nobuyuki Nishikiori, Jean–Louis Arcand, Edith Patouillard,

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richard.white@lshtm.ac.uk
The TB Vaccine Pipeline

Strengths, Weaknesses, Opportunities & Threats

GVIRF Webinar
New Tuberculosis Vaccines for Adults & Adolescents
22 February 2024

Mark Hatherill
South African Tuberculosis Vaccine Initiative (SATVI)
University of Cape Town
WHO COVID-19 vaccine tracker

1. Number of vaccines in clinical development: 183
2. Number of vaccines in pre-clinical development: 199

3. Candidates in clinical phase

<table>
<thead>
<tr>
<th>Platform</th>
<th>Candidate vaccines (no. and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>Protein subunit 23 46%</td>
</tr>
<tr>
<td>VVnr</td>
<td>Viral Vector (non-replicating) 3 6%</td>
</tr>
<tr>
<td>DNA</td>
<td>DNA 2 4%</td>
</tr>
<tr>
<td>IV</td>
<td>Inactivated Virus 10 20%</td>
</tr>
<tr>
<td>RNA</td>
<td>RNA 7 14%</td>
</tr>
<tr>
<td>VVr</td>
<td>Viral Vector (replicating) 1 2%</td>
</tr>
<tr>
<td>VLP</td>
<td>Virus Like Particle 3 6%</td>
</tr>
<tr>
<td>VVr + APC</td>
<td>VVr + Antigen Presenting Cell 0 0%</td>
</tr>
<tr>
<td>LAV</td>
<td>Live Attenuated Virus 1 2%</td>
</tr>
<tr>
<td>VVnr + APC</td>
<td>VVnr + Antigen Presenting Cell 0 0%</td>
</tr>
<tr>
<td>BacAg:SpV</td>
<td>Bacterial antigen-spore expression vector 0 0%</td>
</tr>
</tbody>
</table>

COVID-19 Vaccine Development

- >40 efficacy trials
- >400,000 volunteers
- 12 WHO approved vaccines in <3 years

Grana et al, Efficacy and safety of COVID-19 vaccines, Cochrane Database of Systematic Reviews 2022

Reid et al, The Lancet Commission on Tuberculosis, Lancet 2023

183 COVID-19 vaccines in clinical pipeline
50 COVID-19 vaccines in Phase 3 alone

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

30th March 2023
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.

Strength:
Diversity of vaccine platforms

Weakness:
Few candidates (14 + BCG)
Few novel antigens

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/
Entering large Phase 3 licensure trial (Q1 2024): Results expected 2028
20,000 adolescents and adults aged 15-44 years (20,000 IGRA+; 1,000 IGRA- and HIV-)

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

Modelling projections M72/AS01\textsubscript{E} 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
- "mTB" People without mTB infection
- "mTB" People with mTB infection
- aTBD People with active TB disease
- MDR People with MDR-TB
- cTB People cured of active TB

**Primary endpoint**
- Sf Safety
- POI Prevention of Infection
- POD Prevention of Disease
- POR Prevention of Recurrence
- Tmp Therapeutic

**Strength:**
Several candidates in Phase 2b-3 (5 + BCG)
(9 + BCG)
(BNT164a/b1)
(POI; POR; Tx; POD HHC)

**Weaknesses:**
Few candidates in active trials
Few new candidates in Phase 1-2
“Non-traditional” efficacy trials

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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.nexttbvaccines.org/tb-vaccine-pipeline/](http://www.nexttbvaccines.org/tb-vaccine-pipeline/)

Last update: 28 September 2023
**Opportunity:** Efficacy results positive (2024 - 2028) ➔ 😊 funder/stakeholder sentiment, risk tolerance

**Threat:** Efficacy results negative (2024 - 2028) ➔ ☹ funder/stakeholder sentiment, risk aversion

**Impact investment in new trials?**

➔ study design (POI/POR/POD); study population; vaccine platform (live/inactivated/subunit)

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**Weakness:** “Non-traditional” efficacy trials

May not lead to global licensure

- **POD HHC**
  - VPM1002

- **POR/Tx**
  - H56:IC31; VPM1002; RUTI

- **POI**
  - BCG REVAX; VPM1002
Study Population: Adult TB patients aged 18-60 years, HIV-, pulmonary DS-TB, sputum smear-negative at EOT
Primary objective: Efficacy of H56:IC31 compared to placebo in reducing the rate of recurrent TB disease @ 12 months

NCT03512249

Threat: Efficacy results if negative (2024 - 2028): H56:IC31 POR

Development of the candidate tuberculosis vaccine H56:IC31 ended based on early data from the Prevention of Recurrence (POR) TB Consortium

Vaccine Well Tolerated and Demonstrated Immunogenicity But Did Not Provide Protection Against TB Recurrence. Participants Being Informed; Further Analysis Continues

Impact on stakeholder sentiment?
POR/Therapeutic trials in TB patients? TB vaccine field in general?
### Population-level health and economic impacts of introducing Vaccae vaccination in China: a modelling study

**Opportunity: Efficacy results if positive (2024 - 2028): *M. vaccae* POD**

<table>
<thead>
<tr>
<th>Case definition</th>
<th>Vaccae</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of incident cases</strong></td>
<td><strong>Person-yr follow-up</strong></td>
<td><strong>Rate per 100 person-yr (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Definite pulmonary TB disease</strong></td>
<td>29</td>
<td>8846.3</td>
</tr>
<tr>
<td><strong>Microbiological pulmonary TB disease</strong></td>
<td>8</td>
<td>8858.3</td>
</tr>
<tr>
<td><strong>Smear or culture-positive pulmonary TB disease</strong></td>
<td>7</td>
<td>8858.3</td>
</tr>
<tr>
<td><strong>Definite Xpert MTB/Rif positive pulmonary TB disease</strong></td>
<td>1</td>
<td>8863.2</td>
</tr>
<tr>
<td><strong>Clinical TB disease</strong></td>
<td>21</td>
<td>8851.7</td>
</tr>
</tbody>
</table>

**Source:** BMJ Global Health

**Study completion:** Nov 2017

**NCT01979900**

Anhui Zhifei Longcom

Aged 15 – 65 years

TST 15mm+

6 doses *M. vaccae* vs placebo

Follow up 2 years
**Opportunities:**

- Pending efficacy trials
  - M72/AS01E (Phase 3)
  - MTBVAC (Phase 2b/3)
  - QTP101 (Phase 2b/3)
  - 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)

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**“Recharging” of the TB vaccine pipeline?**
Opportunity: Discover & validate immune correlates of vaccine-mediated protection

Key questions:

Will Phase 2b correlates be validated? (POI BCG REVAX; POD M72/AS01E)

- Single correlate, or signature of multiple correlates?
- Specific to a vaccine/antigen, or generalizable to other candidates?
- Generalizable to other populations?
- Discriminatory performance sufficient to avoid efficacy trial?

Courtesy Elisa Nemes, Tom Scriba, Nicole Frahm
Threat: Lack POD efficacy data IGRA- and pre-adolescents
Disconnect between value proposition vs deliverable data (IGRA-; pre-adolescents)

TB disease incidence (18-25 years)  IGRA+  800 per 100,000  Van Der Meeren NEJM 2018
TB disease incidence (SA adolescents) IGRA-  220 per 100,000  Mahomed, PLoS ONE 2011

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

May never validate IGRA+ POD findings in IGRA-, pre-adolescent population
Threat: Lack POD efficacy data IGRA- and pre-adolescents

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

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**Dose Optimization of H56/IC31 Vaccine for Tuberculosis-Endemic Populations**
A Double-Blind, Placebo-controlled, Dose-Selection Trial

**Unpublished data ClinicalTrials.gov NCT02933281**

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**A Phase I/II Trial of the New Tuberculosis Vaccine, MVA85A, in HIV- and/or Mycobacterium tuberculosis-infected Adults**

**Unpublished data ClinicalTrials.gov NCT02933281**

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

**Safety and immunogenicity of candidate vaccine M72/AS01E in adolescents in a TB endemic setting**

Adam-Preu-Nicholou[1,2], Henrik Geethakos[3], Wayne Kemp[4], Robert van de Mer[5], Cheryl J. Day[5,6], Erik Jagers[7], Philippe Maillet[7], Mark F. Hubber[8], Opeka Olise-Ayejar[9], Willem Hanekom[10], (The Vaccinia South Africa).

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**H1:IC31 vaccination is safe and induces long-term TNF-a/IL-2 CD4 T cell responses in M. tuberculosis infected and uninfected adolescents:**
A randomized trial

Halie Mouton[11], Simon G. Geelhoed[12], Benjamin H. Cupo[12], Mohammed Mostafa[12], Francesco Luizi[13], François Kaiserling[14], Hassen Mohamed[15], Samuel T. Collis[16], Hector Ravin[17], Peter Rang[18], Mark Hubber[19], Peter Adegbola[20], Thomas J. Schild[21], (The Shinhovu Study Group).
<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
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<tbody>
<tr>
<td>- Diversity of vaccine platforms</td>
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<tr>
<td>- Several candidates in Phase 2b-3 (5 plus BCG)</td>
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<td>- Lead candidate with efficacy signal (M72/AS01\textsubscript{E})</td>
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<td>- Partially meets WHO PPC (IGRA+)</td>
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<td>- Few novel antigens</td>
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<tr>
<td>- Few candidates (14 plus BCG)</td>
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<tr>
<td>- Few candidates in active trials (9 plus BCG)</td>
<td></td>
</tr>
<tr>
<td>- Few new candidates in Phase 1-2 (BNT164a/b1)</td>
<td></td>
</tr>
<tr>
<td>- &quot;Non-traditional&quot; efficacy trials $\rightarrow$ global licensure?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHANGE</th>
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<table>
<thead>
<tr>
<th>OPPORTUNITIES</th>
<th>THREATS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pending efficacy results if positive (2024-2028)</td>
<td></td>
</tr>
<tr>
<td>- Pending efficacy results if negative (2024-2028)</td>
<td>- Partially meets WHO PPC (IGRA-)</td>
</tr>
</tbody>
</table>
Acknowledgments

Study participants and their communities
Investigators and study teams
Sponsors and funders
Collaborators
Challenges in TB Vaccine Product Development

GVIRF Webinar

Ann M. Ginsberg, MD, PhD
22 February 2024
Urgent need vs. substantial challenges
TB Vaccine Development’s Three ‘Valleys of Death’

**VALLEY OF DEATH #1**
- **Discovery/Preclinical**
  - Complex multi-stage disease
  - Pathogen expressing ~4000 antigens
  - Protective antigens not fully known
  - Lack of validated animal model
  - Only partial understanding of protective immunity
  - Lack of validated correlate of protection
- **Early Clinical Testing**
  - Dose and regimen selection based on imperfect knowledge
  - No established human challenge model

**VALLEY OF DEATH #2**
- **Late Clinical and Licensure**
  - No validated correlate of protection/surrogate endpoint
  - High cost of late-stage clinical trials
  - Efficacy trials large, long and expensive
  - Limited subnational epi data to support trial designs
  - Limited experienced global site capacity to conduct multiple, simultaneous late-stage efficacy trials
  - Variable regulatory requirements across NRAs and multinational regulatory bodies; long regulatory timelines; variable experience with TB vaccine clinical trials across NRAs

**VALLEY OF DEATH #3**
- **Implementation and Access**
  - Inadequate funding and political will; market failure
  - Label extensions require additional large trials
  - Uncertain market and procurement mechanism
  - Unclear sources and funding mechanisms

Inadequate mechanisms in place to sustainably deliver adolescent/adult vaccines

---

Discovery and Early Development Challenges

- Complex multi-stage infection and disease
- Complex pathogen expressing ~4000 antigens
- Full complement of protective M.tb target antigens not yet known
- Lack of validated nonclinical model predictive of human protection
- Only partial understanding of protective immune mechanisms
- Lack of validated correlate of protection in animal models or humans

➤ These challenges mean TB vaccine discovery is still largely empiric

- Inadequate funding for R&D (~1/8th of HIV and 1/1000 of COVID-19 vaccine R&D investments)

➤ Above challenges plus lack of strong market driver limit pharma interest and investment

Current status: relatively small, inadequately diverse, “inverted” pipeline of clinical candidates
Clinical Development and Licensure Challenges

First ‘valley of death’ – moving from preclinical into human testing – challenging to build a convincing preclinical dataset to ensure funding

Dose and regimen selection based on imperfect knowledge (no vaccine-induced CoP)

No established human challenge model (some in development; see McShane presentation)

Second ‘valley of death’ – advancing into efficacy trials and late-stage development

Due to chronic nature of disease (slow course; only 5-10% of infected individuals progress to active disease; ¼ of world tests positive by skin test or IGRA; ~10 million cases of active disease per year=0.125% of world population), clinical trials to evaluate vaccine efficacy are large and long and therefore expensive – leads to “2nd valley of death” (moving from early phase clinical testing of safety and immunogenicity – to efficacy trials)

Limited subnational epi data to support trial designs

Limited experienced global site capacity to conduct multiple, simultaneous late-stage efficacy trials

Variable regulatory requirements across NRAs and multinational regulatory bodies; long regulatory timelines; variable experience with TB vaccine clinical trials across NRAs

Extension of label post-initial licensure to additional age groups, geographies, etc. will require additional large trials until a CoP is identified and validated for regulatory endpoint use

CoP = Correlate of Protection; IGRA = Interferon-Gamma Release Assay (blood test for prior exposure to M.tb)
Challenges from Licensure to Implementation

➢ Priority for development is vaccine(s) to prevent TB disease in adolescents and adults

Third ‘valley of death’ - ensuring sustainable implementation and access
Little to no experience and infrastructure to efficiently deliver vaccines to adolescents and adults in most countries
Relatively few high-burden countries are GAVI-eligible but all are LMICs
Uncertain demand (no new TB vaccine in 100 years; few adolescent/adult vaccines for any disease in LMICs)
Unclear procurement and delivery/implementation strategy(ies)

Recent landscape analysis conducted by WHO with Boston Consulting Group identified six key gaps in preparation for successful implementation:

Key gaps identified from interviews:
1. Global coordination & consensus on goals, expectations & how to deal with uncertainties
2. Finance across the value chain (both global & country-specific), particularly for procurement & delivery
3. Manufacturing: how to act given the complexity of decision-making and uncertainty
4. Awareness & alignment on Vx candidates for adults & adolescents, need / impact, & timelines outside immediate community
5. Country-specific data (e.g., on demand, priorities, hesitancy, implementation considerations etc.) for adults & adolescents
6. Delivery, health systems readiness & engagement (including e.g., supply chain, workforce & targeted / tailored comms for adults & adolescents)
Much to do - but amazing progress

For the first time in history:

Multiple candidates in late-stage clinical development - representing a variety of vaccine platforms and express varying antigens and adjuvants to drive protection, including whole mycobacterial genomes – so multiple “shots on goal”

Extensive correlates of protection discovery ongoing which could enable future immuno-bridging / surrogate trial endpoints

Multiple R&D funders at the table

Increasing advocacy, community engagement and partnership in developing vaccines and preparing for success

WHO strongly engaged, including establishment of a ministerial level TB Vaccine Accelerator Council

GAVI, Global Fund, other multilaterals paying attention and along with other implementers beginning to come together to plan and prepare

Policymakers at global, regional and national levels beginning to prepare, including exploring best ways to integrate adolescent/adult TB vaccines into existing healthcare systems
Thank you!
Status of correlates development for TB vaccines

Nicole Frahm, PhD
Head of Biomarker Development

GVIRF Webinar:
New Tuberculosis Vaccines for Adults and Adolescents: Progress, Prospects, and Perspectives
February 22\textsuperscript{nd}, 2024
Why do we need correlates of protection (CoP)?

• New TB vaccines that can protect adolescents and adults are urgently needed
• TB vaccine development is challenging for many reasons:
  / There is no animal model that predicts prevention of TB disease
  / Incidence rates are highly heterogeneous and relatively low, thus large clinical endpoint trials are needed to demonstrate vaccine efficacy
• There is limited interest in industry to invest in TB vaccine R&D because programs cannot be de-risked prior to spending hundreds of millions on a Phase 3 program
• If a CoP for prevention of TB disease were identified, confirmed, and accepted by health authorities for licensure of novel TB vaccines, Phase 3 trials could be much smaller and less costly
Assumptions regarding mechanisms of protection

• There is consensus that TB-specific T cells likely play a major role in protection from TB disease
  / Mouse and human data point to IFN-γ as a major mediator of protective immunity; but...
  / Data from the investigational MVA85A vaccine trial suggest IFN-γ may be necessary but not sufficient for protection

• Immune responses beyond IFN-γ-expressing T cells likely contribute to protection
  / Antibody responses may contribute to protection based on new data in humans and NHP
  / IV BCG vaccination points to IL-17 as critical
  / BCG is known to induce epigenetic modifications that afford some level of protection beyond TB
  / Non-classical T cells may also play a role

A comprehensive assessment of immune responses induced by vaccination and their association with protection in human clinical trials would be valuable to provide guidance for vaccine development
Opportunity: 2018 was the year of TB vaccines

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

Tait et al, NEJM 2019, DOI: 10.1056/NEJMc2001364

Two vaccine trials with ~50% efficacy and established sample repositories allowed for the creation of the TB Immune Correlates Program

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Caveat: CoP are defined for a specific “P” and are often vaccine platform-dependent

- **BCG revaccination**
  - IGRA-negative adolescents
  - Protection from sustained infection
    - Measured as sustained QFT conversion
  - Complex vaccine with ~4000 ORFs
    - Intrinsically adjuvanted

- **M72/AS01<sub>E</sub> vaccination**
  - IGRA-positive adults
  - Protection from pulmonary TB disease
    - Measured as microbiologically confirmed pulmonary TB in participants with clinical symptoms
  - Defined vaccine consisting of 2 *Mtb* ORFs
    - Adjuvanted with AS01<sub>E</sub>

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

Tait et al, NEJM 2019, DOI: 10.1056/NEJMc2001364
The quest for vaccine-induced immune correlates of protection against tuberculosis

Elisa Nemes, Andrew Fiore-Gartland, Cesar Boggiano, Margherita Coccia, Patricia D’Souza, Peter Gilbert, Ann Ginsberg, Ollivier Hyrien, Dominick Laddy, Karen Makar, M. Juliana McElrath, Lakshmi Ramachandra, Alexander C. Schmidt, Solmaz Shotorbani, Justine Sunshine, Georgia Tomaras, Wen-Han Yu, Thomas J. Scriba, Nicole Frahm; the BCG Correlates PIs Study Team & the M72 Correlates PIs Study Team
Nemes and Fiore-Gartland, “The quest for vaccine-induced immune correlates of protection against tuberculosis”. Vaccine Insights. 2022
Criteria for prioritization of assays and primary markers

- Every readout is measured from the same samples
- Samples: pre- and post-vaccination
  - 24 BCG and 12 placebo recipients, Day 0 vs. Day 70
  - 40 M72 and 10 placebo recipients, Day 0 vs. Day 37
- We devised statistical criteria for identifying biomarkers that have high potential to be detected as a CoP
  1. Robust vaccine-induced effect
  2. Broad, biologically-relevant dynamic range among vaccine recipients after vaccination
  3. Low temporal variability (among placebo recipients)
  4. Some pre-vaccine variability expected
  5. Readouts should occupy their own niche of immunologic space (low correlation)
  6. Low technical measurement error

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Potential confirmation of candidate CoP

Gates MRI clinical trials

- **BCG Revaccination (TBV01-201)**
  - 1800 IGRA-negative adolescents randomized 1:1 to receive BCG or placebo in South Africa
  - Primary endpoint: prevention of sustained IGRA conversion
  - Biospecimen collection consistent with C-040-404
  - Clinicaltrials.gov NCT 04152161

- **M72/AS01\textsubscript{E} (TBV02-301)**
  - Planned: 20,000 adolescents and adults randomized 1:1 to receive 2 doses of M72/AS01\textsubscript{E} or placebo
  - Primary endpoint: prevention of bacteriologically confirmed pulmonary TB
  - Biospecimen collection consistent with C-041-972
  - Clinicaltrials.gov NCT06062238
Acknowledgments

Leadership Team

Elisa Nemes
Thomas J. Scriba
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- Saman Baral
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- Angelina Sharak
- Sheetal Sawant

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- Natasha Haulman

**LUMC**
- Krista E van Meijgaarden

**Seattle Childrens Hospital**
- Johannes Nemeth
Identification of potential new TB target antigens using T-cell repertoires.

New Tuberculosis Vaccines for Adults and Adolescents, Progress, Prospects, and Perspectives

Part 3: Innovation and new tools in TB vaccine development

Munyaradzi Musvosvi

22 Feb 2024
Challenge: Which antigens to include?

- TB has over 4000 possible vaccine targets

Cole et al., 1998  
Bertholet et al., 2008
Is control of M.tb infection associated with certain mycobacteria-specific T cell clonotypes?

![Diagram showing the progression of M.tb infection, control, and active disease with 'Controllers' and 'Progressors' categories. The 'Controllers' remain healthy, while 'Progressors' progress to active TB. 'Good' and 'Bad TCR' indicate specific T cell clonotypes related to disease control and progression.]

**M.tb infection**

- **Controllers** → **Remain healthy** → **M.tb infection** → **Progressors** → **Active Disease**

- Priority vaccine antigen
  - "Good" TCR
  - "Bad TCR"
Identifying M.tb-specific T cell receptor (TCR) sequences.
Identifying differentially abundant M. tb TCR clusters in controllers and progressors.

Number of donors with sequence

3.4% 0.6% 96.0%

GLIPH2 clusters TCRs with likely shared specificity

CDR3β
CASSVALSNYGYTF
CASSVALFSNTQYF
CASSVALLAGTQYF
CASSVALSGSGYTF
CASSVALFGETQYF
CASSVALGAGEQYF
CASSVALAGANGYTF

Compare cluster frequencies in controllers and progressors

Controller Progressors

0.050
0.015
0.012
0.009
0.006
0.003
0.000
Identifying differentially abundant M.tb TCR clusters in controllers and progressors.

Controllers had higher frequencies of CD4 against epitopes to PE13, CFP-10, WbbL1, and PPE18.
Take home message 1

- We identified dozens of M.tb TCR specificity groups that associated with controllers or progressors.

- This approach has applications for clinical studies of specific T cell responses to vaccination, infection, and other immunological indications.

- May represents a platform for rational antigen selection for candidate subunit vaccines.
Proof of concept study: Immunogenicity

C3HeB/FeJ (Kramnik)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>-</td>
</tr>
<tr>
<td>Mix of PE13/PPE18/CFP-10/WbbL1</td>
<td>2.5µg/2.5µg/2.5µg/2.5µg</td>
</tr>
</tbody>
</table>
Proof of concept study: Immunogenicity

mix (CWPP) mRNA = mix of PE13/PPE18/CFP-10/WbbL1
Day 35 ex vivo stimulation of splenocytes from mice

Preliminary data
Proof of concept study: Immunogenicity (polyprotein constructs)

Preliminary data
TITAN-specific T cell response in uninfected adults, M.tb infected adults, and TB patients.
Take home message 2

- Preliminary preclinical data shows promising immunogenicity.
- Selected 2 priority polyprotein mRNA constructs.
- Murine challenge experiments are ongoing.
- Assessment of baseline antigen-specific response in IGRA-, IGRA+, and persons with active TB is ongoing.
Thomas Scriba
Monika Looney
Virginie Rozot
Constance Schreuder
Tim Reid
Onke Nombida
Michelle Fisher
Elisa Nemes
Ashley Veldsman
Pia Steigler
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Anele Gela
Mark Hatherill
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Patrick Arbuthnot
Njabulo Mnyandu

Bill & Melinda Gates Foundation
ADVANCES IN MODELS TO EVALUATE NEW TB CANDIDATES

New TB Vaccines for Adults and Adolescents, Progress, Prospects, and Perspective

David Lewinsohn, MD, PhD
Professor, Pulmonary & Critical Care Medicine

February 22, 2024
Pai, M. et al. (2016) Tuberculosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.76
Prevention of Progression – Standard Models

Arbues et al, Vaccine 2013

Clark et al., JID 2017
Prevention of Infection – Natural Transmission

Wu et al., PNAS 2015

Table 1: Gene expression of transgenic calves differing by transmission route

<table>
<thead>
<tr>
<th>Route</th>
<th>Infection</th>
<th>Mean Log</th>
<th>Mean Fold</th>
<th>Variance</th>
<th>SD</th>
<th>Mean Log</th>
<th>Mean Fold</th>
<th>Variance</th>
<th>SD</th>
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</tr>
</tbody>
</table>

Gupta et al., Frontiers in Cellular Infection Microbiology 2022
Prevention of Infection - Following Challenge

- Wu et al., PNAS 2015
- Plumlee et al., Cell Host and Microbe 2020
- Plumlee et al., PLoS Pathogens 2023

Table 1. Group sizes needed to assess vaccine-mediated protection of detectable infection.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Vaccine efficacy</th>
<th>Minimum sample size per group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90% Power</td>
<td>80% Power</td>
</tr>
<tr>
<td>61.6%</td>
<td>20%</td>
<td>20</td>
</tr>
<tr>
<td>61.6%</td>
<td>30%</td>
<td>112</td>
</tr>
<tr>
<td>61.6%</td>
<td>40%</td>
<td>66</td>
</tr>
<tr>
<td>61.6%</td>
<td>50%</td>
<td>40</td>
</tr>
<tr>
<td>61.6%</td>
<td>60%</td>
<td>20</td>
</tr>
<tr>
<td>61.6%</td>
<td>70%</td>
<td>21</td>
</tr>
<tr>
<td>61.6%</td>
<td>80%</td>
<td>16</td>
</tr>
<tr>
<td>61.6%</td>
<td>90%</td>
<td>12</td>
</tr>
</tbody>
</table>

Minimum sample size required per group for specified power to detect a given vaccine efficacy (prevalence in unimmunized mice assumed to be 61.6%).
Why do we need a human mycobacterial challenge model?

- To provide a biological signal of efficacy with new vaccines
- To identify potential immune correlates of protection
- As a model of the immunobiology of disease
Prevention of Disease Following Infection

Wu et al., PNAS 2015

Kupz et al., PLoS ONE 2016
Nemeth et al., PLoS Pathogens. 2020

Hansen et al., Nature Medicine 2018

Smith et al., eLife 2022
Concluding Remarks

• “Fit for Purpose” Animal Models
  • Prevention of Infection
  • Sterilizing Immunity
• Standardization
• Correlates of Protection
Preparing the pathway for new TB vaccines for adults and adolescents

Demand considerations

Shelly Malhotra
Executive Director, Global Access, IAVI
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Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada) | And many other generous individuals and partners around the world

As of January 2024
In the lead up to launch, several key enablers critical to ensure timely supply of vaccines that meet country needs

**WHO GLOBAL FRAMEWORK FOR COUNTRY INTRODUCTION OF NEW ADOLESCENT AND ADULT TB VACCINES**

- **Vision & Purpose**: A world free of TB, with zero deaths, disease, and suffering due to TB
- **Goals**: Facilitate rapid introduction and scale up of new adult and adolescent TB vaccines

### Milestones
- **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 manufacturers, 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)

### Approach
- **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/CT)
  - Adequate financing
  - Clarity on roles of funding partners (e.g., Gavi, the Global Fund) and procurement partners (e.g., PAHO, UNICEF)
**Manufacturing scale-up requires considerable lead time and expense**

**Scaling up** clinical trial manufacturing for commercial manufacturing continues to pose a significant challenge.

**TIME**
- To build, start-up and validate a facility could take several years (5 to 10 years)

**INVESTMENT COSTS**
- Manufacturing site with capacity 200 M – 300 M doses/year – 50 M USD – 500 M USD

**DIRECT AND INDIRECT OPERATING COSTS (OPEX)**
- Highly specialized work force.
- Administrative & manufacturing overhead, maintenance, revalidation, QMS.
- Alignment of the process among multiple facilities (Tech-Transfer).

**MARKET FACTORS**
- Assessment of market opportunity key to determine optimal capacity and utilization.
- Clear understanding of coverage, delivery strategies, realistic market share needed.
- Delivery strategies such as mass vaccination will require extra production effort for a limited period. (Overcapacity = increased costs/ Undercapacity = not sustainable).

**VACCINE PRICE**
- Manufacturing facility represents a significant fixed and ongoing maintenance cost – scale of investment has implications on vaccine cost & potential price.

To support planning, independently-built forecasting models developed to refine understanding of TB vaccine market and demand

CHAI

- Insights on major factors influencing demand materialization in 5 TB high burden countries
- MAA for M72AS01e assumed to be in 2029
- Indication: POD
- Target age: 16-34 Years*
- Introductions between 2027-2033 and scale up between 2031-2035 in all countries included
- 2 doses needed

IAVI

- Demand analysis for 55 countries, 26 TB high burden countries for global manufacturing planning under different scenarios
- MAA assumed to be in 2029
- Indication: POD
- Target ages 16-60 years initially, then 16-44 years, with varying rates of coverage
- Gradual introduction of countries from 2030 and within country scale up over 5 years
- 1 dose needed (as per MTBVAC target product profile)

*Plll POD trial for M72/As01e as initially planned for 20,000 individuals aged 16-34 years- reference TAG Pipeline report 2021
Different demand assumptions across the models (V1) impact projected supply requirements

Illustrative number of doses required to meet annual demand for a sample of highest burden countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Steady-state, base case no boosters</th>
<th>One-time catch up campaigns, no boosters</th>
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<tr>
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<td>40,000,000</td>
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<td>Viet nam</td>
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IAVI  CHAI

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- Brazil
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IAVI  CHAI

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**Forecasting TB Vaccine Demand meeting to refine understanding of TB vaccine market**

*Union conference, Paris*

*Side meeting November 17, 2023*

## Meeting Objectives

1. Present multi-country/global TB vaccine market demand assessment efforts to understand methodology and assumptions, limitations and gaps.

2. Gather feedback on assumptions to inform forecast refinement

3. Discuss evidence needs and coordination opportunities for demand estimation with key stakeholders

### Participants

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<tr>
<th>Funders and financing partners</th>
<th>BMGF</th>
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<td>Global Fund</td>
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<td>Boston Consulting Group</td>
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<td>Imperial College London</td>
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<td>Johns Hopkins Bloomberg School of Public Health</td>
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<th>Implementation and Country stakeholders</th>
<th>Baylor College of Medicine – Uganda</th>
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<td>Ministry of Health – Brazil</td>
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<td>PATH Ukraine</td>
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<td>National TB program – Uganda</td>
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<td>National TB program – South Africa</td>
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<th>Global advocacy partners</th>
<th>Treatment Action Campaign</th>
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| Global guidance | WHO SAGE, WHO GTB |
Feedback from *Forecasting TB Vaccine Demand* consultation

- **Implementation and delivery assumptions will vary by country** depending on the epidemiology & program delivery channels:
  - Need to engage a broader set of countries and country-based stakeholders.

- **TB vaccination likely to be implemented through the national vaccination programs:**
  - NTPs have limited resources/access to broader populations to support roll out.

- **Initially likely to target the highest risk populations** based on risk/vulnerability, including potentially:
  - PLHIV (on antiretroviral treatment)
  - Populations linked to TB programs - latent TB, household contacts of TB patients, those exposed and tested for TB,
  - Health care workers
  - People living/spending a large proportion of their time in congregate settings e.g. miners, prisoners, correctional services,
  - Those with diabetes mellitus, smokers, and pregnant women (post partum)

- **After initial phase, plan to move to broader (age-based)/routine role** out through delivery linkage points (e.g. schools/universities) to ensure impact.
  - Risk-based approaches not preferred as they may be onerous to implement and stigmatizing.

- **Further data on vaccine hesitancy, acceptability, feasibility, willingness to pay, and programmatic implications** needed.

- **Future iterations should include:**
  - Key product-related aspects based on TPP and pricing considerations
  - Supply constrained scenario-planning
  - Context of other interventions (e.g. long acting TPT) and of a vaccine landscape with multiple options.

*Current forecasts assume constraints posed by the lack of existing delivery pathways—this provides an opportunity and imperative in lead up to launch to strengthen*
Key takeaways and next steps

• Clear understanding of demand for new TB vaccines is critical:
  • To ensure accurate planning for manufacturing scale up
  • To inform volume-based pricing strategies to sustain fragile market while ensuring affordability
  • To inform financing decisions, including potential for de-risking mechanisms for manufacturing scale up
  • To help attract additional commercial manufacturers, as needed

• Additional stakeholder validation of demand forecasts needed:
  • From a broader range of country-specific settings
  • Across key constituencies (TB stakeholders, Immunization stakeholder, providers, implementers, policy-makers, procurers, financing bodies, communities)
  • Future iterations could consider product related factors in more depth, potential pricing scenarios, supply models, and alternative interventions.
  • In parallel, investment in strengthening delivery pathways and more robust evidence generation needed in the lead up to launch.

• Joint consultations planned to further validate demand assumptions (stay tuned!)
SMART4TB:
Efforts to assess TB vaccine readiness

February 2024

Rupali Limaye, PHD and Andrew Kerkhoff, MD
Several TB vaccine candidates are in phase IIb/III trials

TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 16 vaccine candidates in the pipeline as of January 2024, of which 12 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

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

- **Candidate target population**
  - Elderly
  - Adults
  - Adolescents
  - Children
  - Infants
  - People living with HIV
  - Mtb
  - People with Mtb infection
  - aTBd
  - People with active TB disease
  - MDR
  - People with MDR-TB
  - cTB
  - People cured of active TB

- **Trial status**
  - Active trials
  - No active trials

- **Primary candidate indication**
  - POI: Prevention of Infection
  - POD: Prevention of Disease
  - POR: Prevention of Recurrence
  - Thp: Therapeutic

Information reported by vaccine sponsors or found in clinical trial registries or other public sources

Additional information, including the full list of clinical trials for each candidate, can be accessed at the Stop TB Partnership website.
We have a great opportunity to build demand and strengthen health systems for new TB vaccines

- Vaccines do not save lives; *vaccination* saves lives
- Opportune moment: restore trust and confidence in vaccines and health systems *before* vaccine roll-out
- **Inter-disciplinary research** is critical to guide the design and evaluation of targeted strategies to generate and sustain demand as well as improve health system delivery
- **Community engagement** should be at the center for all vaccine preparatory and introduction activities
Y2 Proposed Activities

1) Conduct mixed-methods research in two TB priority countries to assess health facility and systems readiness for TB vaccine delivery (Research Questions 1, 3)

2) Conduct mixed-methods research in two TB priority countries to explore decision-making factors for TB vaccine acceptance (Research Questions 1, 2)

3) Create a repository to hold TB vaccine readiness tools, documents, and resources (Research Questions 1, 2, 3, 4)

4) Undertake advocacy activities around TB vaccine access policy and vaccine R&D (Research Questions 1, 2, 3, 4)

Countries for Y2: South Africa and Kenya

Priority Research Questions

1) What populations and settings will most benefit from the introduction of a new TB vaccine?

2) What are the barriers to access and uptake for those likely to benefit from a TB vaccine, and what may overcome such barriers?

3) What is the state of readiness of local and national health systems to adopt a novel TB vaccine and scale-up TB vaccination?

4) What is the anticipated acceptability, feasibility, cost-effectiveness and epidemiological impact of different TB vaccine implementation strategies in real-world settings?
Activity 1: Assess health facility and systems readiness for TB vaccine delivery

This activity will **assess capacity for vaccine delivery**, including vaccine cold chain, vaccine management, disease surveillance and reporting, injection safety, and waste management, among others.

- **Review health facility and systems readiness tools** related to adult and adolescent to delivery.
- **Develop a checklist** to assess health facility and systems readiness for new TB Vaccines.
- **Administer tool** to a diverse set of health facilities in two states in two countries.
Activity 2: Explore decision-making factors for TB vaccine acceptance

This activity will **explore the demand** for a new TB vaccine through the 5 Cs and BeSD frameworks:

- **Review and develop demand tools** related to adult and adolescent vaccine acceptance
- **Conduct in-depth interviews** with a range of stakeholders, including potential beneficiaries, healthcare providers, and policymakers
- **Perform surveys and choice experiments** among community members and healthcare workers
Y3 Proposed Activities: Co-Creation

- Co-creation process with key stakeholders to operationalize findings from Y2 mixed-methods research into outputs for countries to prepare for TB vaccines.
  - Through multiple stakeholder workshops, we will use data collected from the first year of engagement to identify key outputs needed for country readiness to deliver a TB vaccine to adults and adolescents
  - Stakeholder types for co-creation engagement: potential vaccine beneficiaries, NITAG members, health care providers, community leaders, EPI, NT

- Many potential outputs – meant to be most useful to local and national stakeholders
  - Supporting the development of implementation plans
    - Including tailored implementation and delivery strategies
  - Supporting the development of communication and demand strategies
  - Supporting the development of health systems strengthening plans
  - Policy briefs for NITAG
SMART4TB is made possible by the generous support of the American people through the United States Agency for International Development (USAID) and is implemented under cooperative agreement number 7200AA20CA00005. The consortium is managed by prime recipient, Johns Hopkins University.

Thank you!
WHO activities to accelerate new TB vaccine development and use

Birgitte Giersing, PhD
Vaccine Product & Delivery Research
Dept of Immunization, Vaccines & Biologicals, WHO

GVIRF webinar on New TB Vaccines
22nd February, 2024
TB remains the second leading cause of death from a single infectious agent, after Covid-19

In 2022, an estimated 10.6 million people fell ill with TB.

1.3 million people died.

COVID severely impacted the ability to detect cases and treat, causing an excess 0.5 million deaths between 2020–2022.

We urgently need a vaccine that prevents against TB disease.

*167 000 deaths among people living with HIV
A catalytic time for new TB vaccine development

**Target population**

**Vaccine target product attributes**

**Regulatory and implementation strategy**

Source: Stop TB Partnership, [https://newtbvaccines.org/pipeline-sortable/](https://newtbvaccines.org/pipeline-sortable/)
Where TB is most common – many are middle-income economies
There are two pathways to recommendation and use

**National** regulatory approval and implementation pathway:

1. Discovery & preclinical
2. Early clinical
3. Clinical Proof-of-Concept
4. Pivotal Efficacy study
5. Registration
6. National policy
7. Procurement
8. Introduction & Implementation
9. Sustainable Supply

**Middle income self-procuring countries**

**Global** regulatory approval and implementation pathway:

1. Discovery & preclinical
2. Early clinical
3. Clinical Proof-of-Concept
4. Pivotal Efficacy study
5. Registration
6. WHO global policy & PreQual.
7. Effectiveness/Pharmacovigilance
8. Global/regional Financing
9. Global/regional Procurement

**Countries seeking financial support / pooled procurement**
Why 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
What is WHO doing to address these challenges?

Identifies the key barriers to TB vaccine R&D, and potential ways in which they might be overcome.

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.

These documents can be navigated to from the WHO Vaccine Product and Delivery Research webpage.
WHO global framework to prepare for country introd’n of new adolescent and adult TB vaccines
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.
Global alignment and co-ordination of stakeholders will be key

Aims to facilitate the development, testing, authorization, and use of new TB vaccines

Work-planning underway:
- To leverage, rather than duplicate, existing initiatives
- To help address gaps that require this kind of unique, high-level forum
- Address a clear ask for a focus on financing mechanisms and market solutions.