Webinar

TB Vaccine Development: The Next Chapter Starts Now


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TB Survivor and Advocate

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Early Career Researcher

Thursday, April 13
8:00 am NYC, 2:00 pm Cape Town/Geneva
5:30 pm New Delhi, 7:00 pm Jakarta
The TB Vaccine Pipeline
Vaccine Candidates and Clinical Trials Advocates Should Know

Mike Frick
TB project co-director

TAG
Treatment Action Group
Agenda

2 opening questions

3 vaccine development strategies

6 views of the pipeline

4 candidate close-ups

Why do we need new TB vaccines when we have BCG?

Because BCG is >100 years old and it hasn’t stopped the epidemic!
**BCG: the only existing vaccine against TB**

- Bacillus Calmette–Guérin (BCG): developed by Albert Calmette and Camille Guérin in France in early 1900s (interrupted by WWI).
- First introduced into human use in 1921.
- BCG is a live attenuated form of *Mycobacterium bovis*, the organism that causes TB in cattle.
- Part of the EPI package and given to infants soon after birth. Believed to be the mostly widely administered vaccine in human history.
- Protects children against severe forms of TB (e.g., TB meningitis, miliary TB, disseminated TB), but offers highly variable protection against pulmonary TB in adolescents and adults, who account for most TB transmission.
Infant BCG vaccination and risk of pulmonary and extrapulmonary TB throughout the life course: a systematic review and individual participant data meta-analysis

• Analyzed individual-level data from 68,552 TB contacts in 26 case-contact cohort studies from 17 countries (all published within the last 20 years). Found that:
  • infant BCG vaccination was effective in preventing all TB, pulmonary TB, and death, especially among younger children.
  • the overall effectiveness of BCG against all forms of TB was 18%. The protective effect of BCG against TB waned in participants ≥ 5 years.
  • BCG provided >80% protection against death, an effect that lasted through age 14.

“These results suggest that infant BCG vaccination, although important to young children who are at high risk of tuberculosis, does not prevent adult-type cavitary tuberculosis and is therefore insufficient to impede the tuberculosis epidemic, providing further evidence that novel vaccines are urgently needed.”

Martinez et al, 2022 10.1016/S2214-109X(22)00283-2
Why is it taking so long to develop new vaccines against TB?

Because we’re running the hurdles, not a straightaway sprint. There are multiple obstacles – scientific, political, financial – that we have to jump over, knock down, or clear away.
TB vaccine strategies

Currently, there are three overarching strategies guiding TB vaccine development efforts. Each is known by the primary endpoint of interest.

- **POI** = prevention of infection
- **POD** = prevention of disease
- **POR** = prevention of recurrence (relapse or reinfection)
## The Pipeline

*the bird’s eye view*

<table>
<thead>
<tr>
<th>16</th>
<th>The pipeline contains ~16 vaccine candidates including 6 in or preparing for phase III trials.</th>
</tr>
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<tbody>
<tr>
<td>&gt;75,000</td>
<td>The field is mounting multiple phase III trials that will together enroll over 75,000 people. (The most since the middle of the 20th century!)</td>
</tr>
<tr>
<td>Dozens</td>
<td>These phase III trials will bring TB vaccine science to over a dozen countries.</td>
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<tr>
<td>100,000s</td>
<td>Investigators will collect hundreds of thousands of participant samples that will guide next-generation vaccine development and immunology and other basic science research on TB.</td>
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<tr>
<td>∞</td>
<td>Ongoing and planned phase II and III trials will enroll diverse populations of people at risk of TB, including PLHIV, children, household contacts of people with TB, people treated for TB disease, and people with MTB infection and those without.</td>
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The Pipeline by name

**Phase I**
- TB/FLU-05E
  - Also TB/FLU-01L & TB/FLU-04L
- AdHu5Ag85A
- BNT164

**Phase IIa**
- ChAdOx1.85A + MVA85A
- AEC/BC02

**Phase IIb**
- H56:IC31
- DAR901
- ID93/GLA-SE
- QTP101
- RUTI

**Phase III**
- MIP (Immuvac)
- VPM1002
- M72/AS01E
- MTBVAC
- GamTBVac
- BCG (re)vaccination

Vaccine candidate name

Very little in early phases!
<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>TB/FLU-05E</td>
<td>ChAdOx1.85A + MVA85A</td>
<td>H56:IC31</td>
<td>MIP (Immuvac)</td>
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<td>AdHu5Ag85A</td>
<td>AEC/BC02</td>
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<td>VPM1002</td>
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<tr>
<td>BNT164</td>
<td></td>
<td>ID93/GLA-SE</td>
<td>M72/AS01E</td>
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</table>

- **Protein/adjuvant**
- **Mycobacterial live attenuated**
- **Mycobacterial inactivated**
- **Viral vector**
- **mRNA**

The Pipeline *by type*
The Pipeline

by developers, sponsors, and funders
The Pipeline
by clinical trials
<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB/FLU-05E</strong>&lt;br&gt;Also TB/FLU-01L and TB/FLU-04L&lt;br&gt;• Phase I trial TBA</td>
<td><strong>ChAdOx1.85A + MVA85A</strong>&lt;br&gt;• NCT03681860</td>
<td><strong>H56:IC31</strong>&lt;br&gt;• NCT03512249 (POR)</td>
<td><strong>MIP</strong>&lt;br&gt;• CTRI/2019/01/017026 (POD)</td>
</tr>
<tr>
<td><strong>AdHu5Ag85A</strong>&lt;br&gt;• NCT02337270</td>
<td><strong>AEC/BC02</strong>&lt;br&gt;• NCT04239313</td>
<td><strong>DAR901</strong>&lt;br&gt;• NCT02712424 (POI)</td>
<td><strong>VPM1002</strong>&lt;br&gt;• CTRI/2019/01/017026 (POD)&lt;br&gt;• NCT04351685 (POI)&lt;br&gt;• NCT03152903 (POR)&lt;br&gt;• NCT05539989</td>
</tr>
<tr>
<td><strong>BNT164</strong>&lt;br&gt;• NCT05537038&lt;br&gt;• NCT05547464</td>
<td></td>
<td><strong>ID93/GLA-SE</strong>&lt;br&gt;• A5397/HVTN603 (Rx vax)&lt;br&gt;• NCT03722472</td>
<td><strong>M72/AS01E</strong>&lt;br&gt;• Phase III trial TBA (POD)&lt;br&gt;• NCT04556981 (PLHIV)&lt;br&gt;• NCT05190146 (Epi study)</td>
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<td></td>
<td><strong>QTP101</strong>&lt;br&gt;• Phase IIb/III TBA (POD)</td>
<td><strong>MTBVAC</strong>&lt;br&gt;• NCT04975178 (POI)&lt;br&gt;• Phase I/II in PLHIV TBA&lt;br&gt;• Phase III trial in adults &amp; adolescents TBA (POD)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td><strong>GamTBVac</strong>&lt;br&gt;• NCT04975737 (POD)</td>
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<tr>
<td><strong>ChAdOx1.85A + MVA85A</strong>&lt;br&gt;• NCT03681860</td>
<td><strong>ID93/GLA-SE</strong>&lt;br&gt;• A5397/HVTN603 (Rx vax)&lt;br&gt;• NCT03722472</td>
<td><strong>RUTI</strong>&lt;br&gt;• NCT04919239 (Rx vax)&lt;br&gt;• NCT05455112 (Rx vax)</td>
<td><strong>BCG (re)vaccination</strong>&lt;br&gt;• NCT05330884 (POD)&lt;br&gt;• NCT04151161 (POI)&lt;br&gt;• NCT04453293 (pre-travel)&lt;br&gt;• NCT05539989</td>
</tr>
</tbody>
</table>

Previous, current, or planned studies in PLHIV or that include PLHIV in **bold**

The Pipeline

by PLHIV inclusion
"Trials of TB vaccine candidates should include people living with HIV . . . "

"All people with HIV participating in TB vaccine trials must be on ART."

"TB vaccine trial participants with HIV should either previously have completed TB preventive treatment before enrollment or be offered TPT during the study."
Clinical trials of tuberculosis vaccines in the era of increased access to preventive antibiotic treatment

Molebogeng X Rongaka, Mike Frick, Gavin Churchyard, Alberto L. Garcia-Bastón, Mark Hatterill, William Hanekom, Philip C. Hill, Yoshihisa Hanada, Matthew Quin, Johan Verhovens, Richard G White, Frank Cabezas

A  All-comers design

Mixed population: participants not eligible or eligible for TPT

Not eligible

Eligible

TPT?

Vaccine versus Placebo

B  Decliners or recent-takers design

Participants declined or recently completed TPT

Vaccine versus Placebo

C  Direct comparison (replacement)

Participants eligible for TPT

Vaccine versus TPT

D  TPTVacc design

Participants eligible for TPT

TPT + Vaccine versus TPT + Placebo
VPM1002

- VPM1002 is a live vaccine based on recombinant BCG (i.e., BCG with purposeful genetic modifications to provide better safety and efficacy).
- Developed at the Max Planck Institute in Germany, licensed to Vakzine Projekt Management (VPM), which then provided an exclusive sublicense to the Serum Institute of India (SII).
- Three ongoing phase III trials.

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD</td>
<td>Completed enrollment in a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 and MIP (vs. placebo) in preventing TB disease (pulmonary or extrapulmonary) among 12,721 household contacts (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026). Secondary objectives include efficacy evaluation for POI. Primary completion: 2022.</td>
</tr>
<tr>
<td>POI</td>
<td>Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 (vs. BCG) in preventing MTB infection among 6,940 newborns (HIV-exposed and uninfected eligible) in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685). Primary completion: November 2022.</td>
</tr>
<tr>
<td>POR</td>
<td>Undergoing a phase II/III trial evaluating efficacy, safety, and immunogenicity of VPM1002 (vs. placebo) in preventing TB disease recurrence (pulmonary or extrapulmonary) in 2,000 HIV-negative adults ages 18–65 years successfully treated for TB in India and Bangladesh (NCT03152903). Primary completion: February 2022.</td>
</tr>
<tr>
<td>Other</td>
<td>Planning for a phase I/II safety/immunogenicity study of VPM1002 or BCG revaccination (vs. placebo) in 480 HIV-positive and HIV-negative pre-adolescents ages 8–14 with and without MTB infection in South Africa (IMPAACTP2035/HVTN604; LEAP).</td>
</tr>
</tbody>
</table>

VPM1002
- CTRI/2019/01/017026 (POD)
- NCT04351685 (POI)
- NCT03152903 (POR)
- IMPAACTP2035/HVTN604

Results this year?  
Results by 2024?
Phase III Trial of VPM1002 and MIP
CTRI/2019/01/017026

- 3 arm study with two experimental vaccine candidates: VPM1002 and MIP.
- The trial will compare VPM1002 and MIP to placebo.
- Primary outcome: POD. “To compare the percentage of confirmed TB cases (PTB and EPTB) in the vaccinated and placebo groups from 2 months after first dose of vaccine till 38 months follow-up period.”
- “Final analysis will be done at the time when 160 incident TB cases are observed in the trial or end of follow up period whichever is earlier.”
- Status: fully enrolled.

>12,700 child, adolescent, and adult participants randomized

Household contacts ≥6 years HIV-negative
M72/AS01E

- Subunit protein/adjuvant vaccine.
- Initially developed by GSK and now being taken forward by the Gates Medical Research Institute.
- Positive efficacy signal in phase IIb trial in Kenya, South Africa, and Zambia.

**49.7% (90% CI: 12.1–71.2) protection against developing bacteriologically confirmed pulmonary TB disease among HIV-negative, MTB-infected adults.**

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M72/AS01E
- Phase III trial TBA (POD)
- NCT04556981 (PLHIV)
- NCT05190146 (Epi study)

M72
- Antigen
  (Gates MRI)

AS01E
- Adjuvant
  (GSK)
M72/AS01E

- **Phase III** study (next slide).
- **MESA-TB**: Safety/immunogenicity study of M72/AS01E in ~400 PLHIV (16–35 years) in South Africa on ART and who have previously taken TB preventive treatment.
  - Co-funded by Wellcome Trust.
  - Participants must have HIV RNA <200 copies/mL at screening and CD4+ cell counts ≥200 cells/µL.
- **Epidemiology study** to prepare for the phase III trial. The study will assess IGRA positivity and TB incidence near potential trial sites.
  - Will enroll 8,000 participants in Bangladesh, Brazil, DRC, Gambia, India, Indonesia, Kenya, Mozambique, Peru, Philippines, South Africa, Uganda, Vietnam, Zambia.
  - Data will be a “global good” available to other vaccine developers and researchers.

Starting soon?

Complete and results expected soon. Will allow PLHIV to enroll in the phase III trial.

NCT04556981

Epi study to prepare for ph. III trial. NCT05190146
Phase III Trial of M72/AS01E
To begin soon

26,000 participants to be randomized

1 M72/AS01E
2 placebo

- Primary objective: Evaluate vaccine efficacy in the prevention of bacteriologically-confirmed pulmonary TB (POD) among participants who are IGRA+ (indicating MTB infection) and HIV-negative.

- Gates MRI hopes to open enrollment in late 2023 or early 2024 and to have results 4–5 years after enrollment begins. ~2028

- Status: preparing to open. A preparatory epi study is underway in ~11 countries.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
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<tbody>
<tr>
<td>IGRA+, HIV-</td>
<td>20,000</td>
</tr>
<tr>
<td>IGRA-, HIV-</td>
<td>4,000</td>
</tr>
<tr>
<td>HIV+</td>
<td>2,000</td>
</tr>
<tr>
<td>Total</td>
<td>26,000</td>
</tr>
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Information as reported by Gates MRI in 2022 TAG Pipeline Report
MTBVAC

- MTBVAC = live attenuated MTB (i.e., a weakened version of the TB pathogen itself!) In this case, the attenuation is the deletion of two genes responsible for virulence (phoP and fadD26).

- In 2022, Biofabri reached an agreement with Bharat Biotech “to guarantee the worldwide production and the supply of the future vaccine in more than 70 countries with a high TB incidence.”
Phase III trial of MTBVAC
NCT04975178

~7,000 infant participants

1. MTBVAC
2. BCG

- Primary outcome: Prevention of TB disease (POD) in healthy HIV-uninfected (HU) and HIV-exposed uninfected (HEU) newborns.

- Infants will be followed for a minimum of 24 months to see how many develop TB disease.

- Status: recruiting.
BCG revaccination

- Earlier phase II study that found BCG revaccination had an estimated vaccine efficacy of 45.4% (95% CI: 6.4–68.1) against sustained IGRA conversion (secondary endpoint).

- Sustained IGRA conversion = an initial conversion from negative to positive (signaling TB infection) and subsequent tests stay positive upon testing three and six months after the initial conversion.

<table>
<thead>
<tr>
<th>POD</th>
<th>Undergoing a phase III efficacy, safety, immunogenicity study of BCG revaccination (vs. TB preventive treatment) among 9,200 BCG-vaccinated, HIV-negative child and adolescent household contacts ages 6 to 18 years in India (NCT05330884; BRIC). Primary completion: June 2025.</th>
</tr>
</thead>
<tbody>
<tr>
<td>POI</td>
<td>Undergoing a phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in 1,820 BCG-vaccinated, MTB-uninfected adolescents aged 10–18 years in South Africa (NCT04151161). Primary completion: April 2023. Undergoing a phase III trial to evaluate the efficacy and safety of pre-travel vaccination with BCG (vs. placebo) among 2,000 BCG-naive, MTB-uninfected adults aged 18–65 years, either healthcare workers or long-term travelers to high-TB-burden countries from the United States (NCT04453293). Primary completion: May 2024.</td>
</tr>
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<td>Other</td>
<td>Planning for a phase I/II safety/immunogenicity study of BCG revaccination or VPM1002 (vs. placebo) in 480 HIV-positive and HIV-negative pre-adolescents aged 8–14 years with and without MTB infection in South Africa (IMPAACTP2035/HVTN604).</td>
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</table>

New trial. First study of vaccine vs. preventive treatment.

Fully enrolled.
Phase IIb study of BCG revaccination
NCT04152161

1,820 adolescents randomized

10–18 years old
BCG-vaccinated
No indication of TB infection (IGRA-)
HIV-negative

- Primary outcome: Number of participants with sustained IGRA conversion from a negative to positive test (POI).
- IGRA used is the QuantiFERON®-TB Gold Plus (QFT).
- Sustained Conversion = initial conversion and QFT positive 3 and 6 months later.
- Status: fully enrolled.
- Sponsor: Gates MRI.
BCG revaccination: comparing trials

<table>
<thead>
<tr>
<th></th>
<th>BCG revax – Phase IIa trial (previous study)</th>
<th>BCG revax Phase IIb trial (current study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant size</td>
<td>989 adolescents</td>
<td>1820 adolescents</td>
</tr>
<tr>
<td>Age</td>
<td>12–17 years old</td>
<td>10–18 years old</td>
</tr>
<tr>
<td>Sites</td>
<td>Worcester, Western Cape</td>
<td>Across South Africa</td>
</tr>
<tr>
<td>TB infection test (IGRA)</td>
<td>QFT Gold</td>
<td>QFT Gold Plus</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>IGRA conversion</td>
<td>Sustained IGRA conversion</td>
</tr>
</tbody>
</table>

What would a positive result mean?
- A positive result from this study could spark a policy change recommending a second dose of BCG in adolescence to protect high-risk people from MTB infection.
- Or it could motivate a phase III POD trial among IGRA-negative people to see if BCG revaccination protects against TB disease.
The mRNA vaccines are coming! (maybe)

Has registered two phase I clinical trials of two investigational vaccines under the name BNT164 (BNT164a1 and BNT164b1).

- NCT05537038 (Germany?)
- NCT05547464 (South Africa)

Each will evaluate safety, reactogenicity, and immunogenicity of three dose levels of the vaccines given in a three-dose schedule.

April 7, 2022: “[Moderna and IAVI] today announced a new collaboration to employ mRNA technology to meet the challenge of a range of global health threats: HIV/AIDS, tuberculosis, antimicrobial-resistant enteric infections, and COVID-19.”

Has started preclinical work on a TB vaccine candidate(s).

Will discuss mRNA and TB vaccines on April 21 during the Hub’s week-long meeting in Cape Town.
Thank you!
mike.frick@treatmentactiongroup.org

And thanks to the Working Group on New TB Vaccines and partners in the TB Vax ARM coalition.

If you would like to learn more about the TB Vax ARM’s activities or join the monthly meetings, email Shaun Palmer at SPalmer@iavi.org.

Want more information from TAG? Join our list here!
POD = prevention of disease

• Most relevant for licensure and scale-up.
• Requires measuring the incidence of clinical – ideally, microbiologically confirmed – TB in the vaccine and placebo/control arms.
• Long, with large sample size, and therefore expensive. Why?
  • Estimated incidence of TB disease in most high-incidence countries is not above 400/100,000 per year, so very large sample sizes are needed in order to measure protective efficacy with sufficient precision.
  • Participants must be followed for several years to see if protection is durable/lasting.
  • These limitations can be (partially) addressed by enrolling participants with TB infection (IGRA+ or TST+) as opposed to people without TB infection.
POI = prevention of infection

• Requires measuring the incidence of infection with MTB in the vaccine and placebo/control arms.

• Not clear if prevention of infection is a licensable endpoint from the perspective of regulators.

• Smaller, cheaper, faster trials. Why?
  • Incidence of TB infection is ~10–20 times higher than incidence of TB disease, so trials can enroll faster and accrue endpoints more quickly than POD trials.

• HOWEVER:
  • No easy way to measure infection. TST and IGRAs do not measure infection directly. Sustained IGRA conversion – negative to positive, with no reversion to negative – is the most common POI endpoint.
  • Not clear if POI signals POD. Only 5–10% of people with TB infection progress to TB disease—does a vaccine prevent infection in individuals who would progress otherwise?