State of the field: TB vaccine clinical research

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South African Tuberculosis Vaccine Initiative
University of Cape Town, South Africa
Conflicts of Interest Declaration

Institutional grants to University of Cape Town to fund multiple clinical trials of nine TB vaccine candidates
<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdHu5Ag85A&lt;sup&gt;b&lt;/sup&gt; McMaster, CanSino</td>
<td><strong>ChAdOx185A-MVA85A&lt;sup&gt;b&lt;/sup&gt;</strong> (ID/IM/Aerosol) University of Oxford</td>
<td><strong>BCG ReVax&lt;sup&gt;c&lt;/sup&gt;</strong> Gates MRI</td>
<td><strong>GamTBvac&lt;sup&gt;d&lt;/sup&gt;</strong> Ministry of Health, Russian Federation</td>
</tr>
<tr>
<td><strong>AEC/BC02&lt;sup&gt;e&lt;/sup&gt;</strong> Anhui Zhifei Longcom</td>
<td><strong>ID93 + GLA-SE&lt;sup&gt;d&lt;/sup&gt;</strong> IDRI, Wellcome Trust, IAVI</td>
<td><strong>DAR-901 booster&lt;sup&gt;e&lt;/sup&gt;</strong> Dartmouth, GHIT</td>
<td><strong>MIP/Immuvac&lt;sup&gt;e&lt;/sup&gt;</strong> ICMR, Cadila Pharmaceuticals</td>
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<tr>
<td><strong>TB/FLU-04L&lt;sup&gt;b&lt;/sup&gt;</strong> RIBSP</td>
<td><strong>H56: IC31&lt;sup&gt;d&lt;/sup&gt;</strong> SSI, Valneva, IAVI</td>
<td><strong>MTBVAC&lt;sup&gt;c&lt;/sup&gt;</strong> Biofabri, TBVI, University of Zaragoza</td>
<td><strong>VPM1002&lt;sup&gt;c&lt;/sup&gt;</strong> SIIPL, VPM</td>
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<tr>
<td><strong>M72/AS01E&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td><strong>RUTI&lt;sup&gt;e&lt;/sup&gt;</strong> Archivel Farma, S.L.</td>
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</tbody>
</table>

<sup>a</sup> Information was self-reported by vaccine sponsors to WHO or to the Stop TB Partnership Working Group on New TB Vaccines.
DIVERSITY OF THE PIPELINE OF TB VACCINE CANDIDATES IN CLINICAL TRIALS

- **Phase 1**
  - M. tuberculosis
  - IC31® antibacterial peptide and a synthetic oligonucleotide
  - ESAT-6
  - Rs260, Rv1913

- **Phase 2A**
  - M. tuberculosis
  - AS01E liposomal formulation of MPL and saponin QS-21
  - Rv0128, Rv1196

- **Phase 2B**
  - M. tuberculosis
  - DEAE-dextran core and CpG oligonucleotide
  - ESAT-6 CFP-10 Ag85A

- **Phase 3**
  - M. tuberculosis
  - Ad Ag85A
  - Ag85A

- **MIP**
  - M. vaccae
  - Phase 2B

- **DAR-891**
  - M. bovis
  - M. africanus
  - Phase 2B

- **RUTI**
  - M. tuberculosis
  - Phase 2A

- **WHOLE CELL MYCOBACTERIA**
  - M. vaccae
  - Phase 3

- **LIVE ATTENUATED**
  - BCG
  - Phase 2B

- **ORIGIN**
  - M. tuberculosis
  - M. bovis
  - M. vaccae

- **SOURCE**
  - Double deletion of phiP-fadD26 virulence genes
  - Loss of >100 genes within RD deletions
  - Same as BCG with urease C deletion and lysterolysis insertion

- **METHOD FOR ATTENUATION/INACTIVATION**
  - Heat
  - Detoxified fragments of M. tuberculosis in a liposomal formulation

- **CONTENT IN M. tuberculosis T-CELL ANTIGENS**
  - ALL present
  - Epitopes in RD regions absent

- **ADJUVANT/VIRAL VECTOR**
  - GLA-SE Glucopyranosyl Lipid A (GLA) in oil-in-water emulsion (SE)
  - Ad Ag85A
  - Chimpanzee adenovirus +MVA

- **CONTENT IN M. tuberculosis T-CELL ANTIGENS**
  - Rv3820, Rv3819, Rv2006, Rv1913
  - Ag85A

Slide courtesy Carlos Martin, Update on TB Vaccine Pipeline, Applied Sciences April 2020
1. The advance of live mycobacterial vaccines
2. Trials including children and people living with HIV (PLHIV)
3. Next steps for M72/AS01\textsubscript{E}
4. What will we do with the BCG REVAX results?
5. The crowded landscape of Therapeutic/POR vaccines
1. The advance of live mycobacterial vaccines

2 candidates entering infant efficacy trials

Multiple indications:

- Infant BCG replacement (POI/POD)
- Adolescent and adult POD
- POR
- COVID-19
Completing: Phase 2a Dose-Defining Safety and Immunogenicity Study of MTBVAC in South African Neonates Living in a High-Burden Tuberculosis-Endemic Region (NCT03536117)

99 newborn infants, randomized BCG or 3 escalating doses MTBVAC, follow-up ends March 2021, select Phase 3 dose

Starting: Randomised, Double-blind Controlled Phase 3 Trial to evaluate the Efficacy, Safety and Immunogenicity of MTBVAC Administered in Healthy HIV unexposed and HIV exposed uninfected Newborns in Tuberculosis Endemic Regions of Sub-Saharan Africa (NCT04975178)

7,000 HIV unexposed and HIV-exposed uninfected newborns, randomized BCG or MTBVAC (dose above), 72m FU for TB
Completed: Study to Evaluate the Safety and Immunogenicity of VPM1002 in Comparison with BCG in HIV-exposed/-Unexposed Newborn Infants in South Africa (NCT02391415), manuscript submitted Lancet Infectious Diseases

Recruiting: A multicenter, phase III, double-blind, randomized, active-controlled study to evaluate the efficacy and safety of VPM1002 in comparison to BCG in prevention of Mycobacterium tuberculosis infection in newborn infants (NCT04351685)

6,940 newborn infants (HIV unexposed and HIV-exposed uninfected) in Gabon, Kenya, South Africa, Tanzania, and Uganda, randomized BCG or VPM1002, FU 36m (POI, POSI; safety; 2° POD)
2. Trials including children

VPM1002
Phase 2b POI (Infants)
POD (HHC)
POR

Planned: Safety & immunogenicity study of VPM1002 vs BCG revaccination vs placebo
DAIDS funded (IMPAACTP2035/HVTN604)
480 children aged 8–14 years, stratified by HIV and IGRA IGRA- and IGRA+; HIV- and HIV+ (ART)

*BCG REVAX
2. Trials including people living with HIV (PLHIV)

Draft Roadmap for developing TB vaccines for people living with HIV (DAIDS: Churchyard, Kublin, Gupta et al)

Changing perception risk (ART)
Necessary include PLHIV prior to Phase 3
BCG and live mycobacterial vaccines (risk:benefit)

VPM1002
Phase 2b POI (Infants)
POD (HHC)
POR

Planned: Safety & immunogenicity study of BCG revaccination vs VPM1002 vs placebo
DAIDS funded (IMPAACTP2035/HVTN604)
480 children aged 8–14 years, stratified by HIV and IGRA
IGRA+ and IGRA-; HIV+ (ART) and HIV-

M72/AS01$_E$
POD

Follow-up: Safety and Immunogenicity of a Mycobacterium Tuberculosis Vaccine M72/AS01E in Participants With Well-controlled HIV (MESA-TB) (NCT04556981)
400 PLHIV aged 16–35 years (ART+ and VL-) in South Africa; → include PLHIV in Phase 3 POD
3. Next steps for M72/AS01\textsubscript{E}

M72/AS01\textsubscript{E} POD

Starting: Epi study 50 sites, 12-15 countries, IGRA prevalence survey (Gates MRI)

Planned: Phase 3 efficacy, safety, and immunogenicity licensure trial, multiple sites and countries, 2023 (Gates MRI)
→ 20,000 adolescents and adults aged 16–34 years, IGRA+(-); include PLHIV
4. What will we do with the BCG REVAX results?

BCG Revaccination

POSI

Follow-up: A Randomized, Placebo Controlled, Observer-Blind, Phase IIb Study to Evaluate the Efficacy, Safety, and Immunogenicity of BCG Revaccination in Healthy Adolescents for the Prevention of Sustained Infection With Mycobacterium Tuberculosis (BCG REVAX; Gates MRI-TBV01-201) (NCT04152161)

1,800 IGRA- SA adolescents (10-18 yr), randomized BCG revaccination or placebo; follow-up 48 months; primary endpoint sustained IGRA+ conversion (QFT-Plus) thru 6 months

Need to validate POI findings in POD trial

Original rationale: green light POD trial BCG revaccination in IGRA- adolescents

TB incidence, sample size, duration, cost?
GamTBvac

POD in IGRA-

Started: Phase 3 Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of the Subunit Recombinant Tuberculosis Vaccine GamTBvac in Preventing the Development of Primary Respiratory Tuberculosis Not Associated With HIV Infection in Healthy Volunteers Aged 18-45 Years (NCT04975737)

7,180 HIV- BCG+ IGRA- adults aged 18–45 years (Russia MoH)
Follow-up 24 months TB disease
5. The crowded landscape of Therapeutic/POR vaccines

**VPM1002**: Recruiting: A Multicenter Phase II/III Double-Blind, Randomized, Placebo Controlled Study To Evaluate The Efficacy And Safety Of VPM1002 In The Prevention Of Tuberculosis Recurrence In Pulmonary TB Patients After Successful TB Treatment (NCT03152903)

2,000 HIV-negative adults aged 18–65 years treated for TB, randomized VPM1002 vs placebo, FU 12 months recurrent TB

**H56:IC31**: Follow-up: Phase 2, Double-blind, Randomized, Placebo-Controlled Study to Evaluate Safety and Efficacy of H56:IC31 in Reducing the Rate of TB Disease Recurrence in HIV Negative Adults Successfully Treated for Drug-Susceptible Pulmonary Tuberculosis (NCT03512249)

900 HIV- adults aged 18–60 years completed DS-TB treatment, randomized H56:IC31 or placebo, FU 12 months recurrent TB

**ID93+GLA-SE**: Planned: Phase IIa/IIb safety/immunogenicity study ID93/GLA-SE as adjunctive therapeutic vaccine DAIDS (A5397/HVTN603.1)

1,500 HIV+ / HIV- patients treated DS-TB, randomized ID93+GLA-SE vs placebo early timepoints in treatment; adverse treatment outcomes (failure; recurrence 12 months)

**RUTI**: Planned: Double-Blind, Randomized, Placebo-Controlled, Phase IIb Clinical Trial to Investigate the Efficacy of RUTI® Therapeutic Vaccination as Adjuvant of Tuberculosis Chemotherapy (NCT04919239)

140 HIV- adults ≥18 years treated DS-/DR-TB; randomized RUTI vs placebo, FU 6 months culture conversion, bacillary load; adverse events
Summary

1. Live mycobacterial vaccines entering infant efficacy trials

2. Plans to include children and adults living with HIV in efficacy trials

3. Preparation M72/AS01\textsubscript{E} Phase 3 POD

4. POD efficacy trials include IGRA-

5. Several Therapeutic or POR trials planned/ongoing
EXTRA SLIDES
# Diversity of Candidates in Clinical Trials

<table>
<thead>
<tr>
<th>Origin</th>
<th>Source</th>
<th>Method for Attenuation/Inactivation</th>
<th>Content in M. tuberculosis T-cell Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis Phase 2A</td>
<td>Rv0125 Rv1196</td>
<td>Heat</td>
<td>?</td>
</tr>
<tr>
<td>M. tuberculosis Phase 2A</td>
<td>ESAT-6 Ag85A</td>
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<td>M. tuberculosis Phase 1</td>
<td>DEAE-dextran core and CpG oligonucleotide</td>
<td>BCG Recombination</td>
<td>Loss of &gt;100 genes within RD deletions</td>
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<td>M. tuberculosis Phase 1</td>
<td>GLA-SE Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (GE)</td>
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<td>M. tuberculosis Phase 2A</td>
<td>Rv3620 Rv3619 Rv2688 Rv1913</td>
<td>MTBVAC</td>
<td>Double deletion of phoF-fadD26 virulence genes</td>
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### Whole Cell Mycobacteria

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<th>Origin</th>
<th>Viral Vector</th>
<th>Adjuvant/Viral Vector</th>
<th>Content in M. tuberculosis T-cell Antigens</th>
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<tr>
<td>M. tuberculosis Phase 2B</td>
<td>M. vaccae</td>
<td>Non-Tuberculous Mycobacteria</td>
<td>Heat</td>
</tr>
<tr>
<td>M. tuberculosis Phase 1</td>
<td>Chimpanzee Adenovirus MVA</td>
<td>Non-Tuberculous Mycobacteria</td>
<td>Heat</td>
</tr>
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<td>M. tuberculosis Phase 2A</td>
<td>M. vaccae M. tuberculosis</td>
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### Live Attenuated

**Courtesy Carlos Martin**

*Update on TB Vaccine Pipeline, Applied Sciences 2020*