The Tuberculosis Vaccine Pipeline

Mark Hatherill

South African Tuberculosis Vaccine Initiative
University of Cape Town, South Africa
### WHO Global Tuberculosis Report 2022

<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>14 candidates + BCG</strong></td>
<td></td>
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<tr>
<td><strong>3 viral vector</strong></td>
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<tr>
<td>Ad5Ag85A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>McMaster, CanSino</td>
<td>BCG revaccination to prevent infection&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;,j&lt;/sup&gt;</td>
<td>GamTBvac&lt;sup&gt;e&lt;/sup&gt; Ministry of Health, Russian Federation</td>
</tr>
<tr>
<td>MVA85&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;,i&lt;/sup&gt;</td>
<td>University of Oxford</td>
<td>Gates MRI</td>
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<tr>
<td><strong>3 inactivated mycobacterial</strong></td>
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<tr>
<td>M. obuense&lt;sup&gt;1&lt;/sup&gt;</td>
<td>DAR-901 booster&lt;sup&gt;f&lt;/sup&gt;&lt;sup&gt;,j&lt;/sup&gt;</td>
<td>Dartmouth</td>
<td>MIP/Immuvac&lt;sup&gt;f&lt;/sup&gt;&lt;sup&gt;,i&lt;/sup&gt;&lt;sup&gt;,j&lt;/sup&gt; ICMR, Cadila Pharmaceuticals</td>
</tr>
<tr>
<td>(DAR-901)</td>
<td>Quaratis U.S. NIH/NIADV</td>
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<tr>
<td>M. tuberculosis&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>(RUTI)</td>
<td>H56: IC31&lt;sup&gt;e&lt;/sup&gt; SSI, Valneva, IAVI</td>
<td>MTBVac&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;,h&lt;/sup&gt; Biofabri, University of Zaragoza, IAVI, TBVI</td>
<td></td>
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<tr>
<td>M. indicus&lt;sup&gt;pranii&lt;/sup&gt;</td>
<td></td>
<td>VPM1002&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;,g&lt;/sup&gt;&lt;sup&gt;,i&lt;/sup&gt;&lt;sup&gt;,j&lt;/sup&gt; SIIPL, BPM</td>
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<tr>
<td>(Immuvac)</td>
<td></td>
<td>BCG vaccination to prevent infection (TiPI)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td><strong>3 live mycobacterial</strong></td>
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<tr>
<td>M. tuberculosis&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>BCG revaccination in children and adolescents (BRio)&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;,i&lt;/sup&gt;&lt;sup&gt;,j&lt;/sup&gt; ICMR</td>
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<tr>
<td>rBCG (VPM1002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mRNA (BNT164)</td>
<td></td>
<td></td>
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<tr>
<td><strong>5 subunit</strong></td>
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<td>ID93+GLA-SE / QTP101</td>
<td>AEC/BC02&lt;sup&gt;e&lt;/sup&gt; Anhui Zhifei Longcom</td>
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Pending: H107 (SSI) first-in-human

https://www.who.int/teams/global-tuberculosis-programme/tb-reports
The TB vaccine pipeline 2012 vs 2022

### 2012

- **12 candidates**
- **Phase 1 dominant**
- 6 candidates no longer in development
- 6 candidates 2012 and 2022 (2 static)
- 8 new candidates

### 2022

- **14 candidates + BCG**
- **Phase 2b-3 dominant**

### 2012 Candidates

- AdAg85A
  - McMaster University
- Hybrid+IC31
  - SSI, Aeras, Intercell
- H56+IC31
  - SSI, Trek, Intercell
- Hyvac/IC31
  - Aeras, Intercell
- AERAS-422
  - Aeras
- M72+AS01
  - GSK, Aeras
- VPM 1002
  - Max Planck, Valzine
- Hybrid+IC31
  - SSI, TBVI, EDCTP, Intercell
- RUTI
  - Archivel Farma, S.L.
- MVA85A
  - Aeras
- AERAS-485
  - Oxford-Emergent Tuberculosis Consortium (OETC), Aeras
- Mw [M. indicus pranii (MIP)]
  - Dept of Biotechnology (India), M/s. Cadila

### 2022 Candidates

- AdHu5Ag85A
  - McMaster, CanSino
- VPM 1002
  - Max Planck, Vakzine
- VPM 1002
  - Max Planck, Valzine
- Hybrid+IC31
  - SSI, TBVI, EDCTP, Intercell
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TB Vaccine Pipeline

Active clinical trials of TB vaccine candidates

There are 11 active clinical trials across nine candidates as of October 2022.

Platform

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant

Trial target population

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

Primary trial indication

- Safety
- Prevention of Infection
- Prevention of Disease
- Prevention of Recurrence
- Therapeutic

8 candidate vaccines + BCG

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/

Last update: 02 February 2023
New TB Vaccines for Infants or Adults?

Adult vaccine strategy with only 40% VE and 5-year protection (R) more impact on TB incidence than by 2050 than Infant vaccine strategy with 80% VE and lifelong protection (L) – due to reduction in *M.tb* transmission

Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries

- **Efficacy = 40%**
- **Duration =**
  - 5 years
  - 10 years
  - 80%
  - Lifelong

**An investment case for new tuberculosis vaccines**

**COSTS AND BUDGET IMPACT**

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<th>VACCINE FOR INFANTS</th>
<th>VACCINE FOR ADOLESCENTS AND ADULTS</th>
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<td>Timeline: 2025–2050</td>
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<tr>
<td>Vaccine price, US$ 4.60</td>
<td><em>(50% efficacy, 80% routine and 70% campaign coverage, 10-year protection, base-case scenario)</em></td>
</tr>
</tbody>
</table>

- **Global costs of vaccine introduction**
  - US$ 11.8 (9.6–16.9) billion
  - US$ 50.5 (38.1–75.9) billion

- **Averted costs for drug-susceptible TB diagnosis and treatment**
  - US$ 342 (223–489) million
  - US$ 3.5 (2.2–5.2) billion

- **Averted costs for drug-resistant TB diagnosis and treatment**
  - US$ 299 (251–351) million
  - US$ 3.2 (2.6–3.8) billion
WHO Preferred Product Characteristics (PPC) for New TB Vaccines

Adolescents & Adults
- 50% or greater efficacy
- Protect with/post- & without/pre- *Mtb* infection
- Protect in diverse geographies
- Safe in PLWHIV, elderly, pregnancy
- 10+ years protection

Infants
- Superior efficacy vs BCG*
- Superior safety vs BCG
- Safe in HIV-infected infants
- 10+ years protection

*Infant BCG
VE 74% Colditz, Pediatrics 1995
VE 59% Mangtani, CID 2014
MTBVAC
Phase 3 POD (infants)

Live-attenuated Mycobacterium tuberculosis vaccine MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial


Started: 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, 72m FU for TB disease

Planned: Safety & immunogenicity (PLWH on ART)
Phase 3 safety & efficacy (adolescents & adults)

ClinicalTrials.gov Identifier: NCT04975178

Recruitment Status: Recruiting
First Posted: July 23, 2021
Last Update Posted: October 12, 2022
VPM1002
Phase 3 POI (Infants)
POD (Household Contacts >6 years)
POR (Adult TB patients)

VPM1002: recombinant urease C-deficient, listeriolyisin-expressing BCG vaccine derived from the BCG Prague strain (minus RD1 and RD2 genes)

Completed: Study to Evaluate the Safety and Immunogenicity of VPM1002 in Comparison with BCG in HIV-exposed/-Unexposed Newborn Infants in South Africa (NCT02391415)
Cotton et al, Lancet Infect Dis 2022
VPM1002 less reactogenic than BCG (injection site ulceration, abscess, scarring) Multifunctional CD4+ and CD8+ T cell responses higher in BCG vs VP1022

Follow-up: 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, safety; 20 POD)
Next Steps…

**BCG Revaccination PO(S)I**

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 FU 48 months; primary endpoint sustained IGRA+ conversion 6 months

Results primary event-driven analysis expected end 2023...

What would we do with positive PO(S)I findings?

POD trial BCG revaccination in IGRA- adolescents?

TB incidence IGRA- lower, sample size +/- 60-70,000

Country-level interest in pragmatic trial with passive follow-up?
**M72/AS01_E**

**POD (adolescents/adults)**

3,575 IGRA+ HIV- adults
Zambia, Kenya, SA

Randomized (1:1)
M72/AS01_E or Placebo
2 doses, 1 month apart

Subclinical TB excluded baseline
3-year follow-up
Micro+ symptomatic TB

<table>
<thead>
<tr>
<th>Year</th>
<th>VE</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>27.4%</td>
<td>−128.8 to 77.0</td>
</tr>
<tr>
<td>Year 2</td>
<td>55.2%</td>
<td>−45.3 to 86.2</td>
</tr>
<tr>
<td>Year 3</td>
<td>60.2%</td>
<td>−27.0 to 87.5</td>
</tr>
<tr>
<td>Years 1-3</td>
<td>49.7%</td>
<td>2.1 to 74.2</td>
</tr>
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</table>

Planned: Phase 3 efficacy, safety, and immunogenicity licensure trial, multiple sites and countries, 2024
26,000 adolescents and adults aged 15-44 years, IGRA+(-); HIV-(+); (POD; 2° POI)
Site selection epi study (IGRA+ rates) multiple countries
Vaccinate before (IGRA-) or after (IGRA+) *M. tuberculosis* exposure?

~23% global population (1.7 billion) Mtb-sensitized, i.e. 77% not…

Risk of TB disease highest within 2 years of exposure

*M.tuberculosis* infection and TB disease rates increase rapidly through adolescence into young adulthood

Target IGRA- pre-adolescents or IGRA+ adolescents and adults?

Houben, PloS Medicine 2016

Abubakar Lancet ID 2018

Wood et al, IJTLD 2010

Wood et al, PLoS ONE 2011
Can subunit vaccination protect Mtb-unsensitized (TST-/IGRA-) individuals against future exposure, infection, and progression to TB disease?

**Adults:** Total frequencies of M72-specific cytokine+ CD4 T cells were higher in TST+ vs TST-.

**Adolescents:** M72/AS01-E induced higher median cytokine+ CD4 T cell responses in IGRA+ vs IGRA-.

**Adults:** Impact of Mycobacterium tuberculosis (M.tb) infection on immunogenicity of H56:IC31. Median frequency of ESAT-6-specific CD4 T cells.

Need an immune correlate of vaccine-mediated protection.
Modelling studies

Vaccine efficacy in IGRA+ populations → greatest reduction in TB incidence by 2050 (IRR 51%, 52%, and 54% in China, South Africa, India)

Vaccine efficacy only in IGRA- populations → moderate reduction in TB incidence by 2050 (IRR 19, 36, and 51% in China, South Africa, India), greater impact in higher-transmission settings

_Harris et al, Sci Transl Med 2020_

*Assumptions: 10-year, 70% efficacy against disease

Optimal strategy?

Vaccine efficacy in both IGRA- and IGRA+ or Combination pre- and post-exposure approaches

*Fig. 3. Vaccine impact by prevention of infection and prevention of disease efficacy. IRR in 2050 by country from a vaccine with 10-year duration of protection for prevention of infection or disease or both, with efficacy in pre- and post-infection populations (PAPI; top row), pre-infection populations (PRI; middle row), or post-infection populations (PSI; bottom row), assumed safe and efficacious in HIV-positive populations, delivered from 2025 as routine vaccination of 9 year olds and as 10-yearly mass campaigns in China, South Africa, and India.*
Why is TB vaccine development so slow?

**Trial duration**

Slow growing Mtb pathogen, slowly progressive TB disease, no epidemic waves, no immune correlates of vaccine-induced protection = long efficacy trials (5+ years)

“**TB vaccine development is not a 100-day dash; it is an endurance marathon that requires an altogether different kind of stamina...**”

*TAG TB Vaccine Pipeline Report 2022*

**Trial-to-trial interval**

Collective stakeholder inertia / lack of risk appetite

M72/AS01 E Phase 2b trial completed 16th November 2018
Final efficacy results published 29th October 2019
Phase 3 trial expected to start in 2024...
Results expected...?
Priorities: diversity of vaccine design and delivery; validated preclinical models; more efficient clinical trials; discovery of immune correlates of protection; understanding of cost-effectiveness, demand and integration into existing programmes

Access new funding streams, reduce financial risk
The case for increased investment in TB vaccine R&D is compelling

TB vaccine with 50% efficacy for adolescents/adults:
- Prevent 37 million TB cases and 4.6 million deaths (2025–2050)
- Avert US$ 3.5 billion DS-TB costs
- Cost-effective in all high TB burden countries
- Cost-saving in 58 of 105 (55%) LMIC
Ongoing

Assessment of full value of new TB vaccines

Development of Evidence Considerations for Vaccine Policy (ECVP)

Development of a Global Framework for Countries to achieve Rapid Introduction and Impact of New TB Vaccines for Adults and Adolescents

Global advocacy efforts

→ drive demand, funding, implementation and uptake of a new, effective TB vaccine
Study participants and their communities
Investigators and study teams
Sponsors and funders
Collaborators
# Diversity of the Pipeline of TB Vaccine 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>
<th>ADJUVANT/VIRAL VECTOR</th>
<th>CONTENT IN M. tuberculosis T-CELL ANTIGENS</th>
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<tbody>
<tr>
<td>M. tuberculosis</td>
<td></td>
<td>Double deletion of phoP-fadD26 virulence genes</td>
<td>ALL present</td>
<td>D93/GLA-SE</td>
<td>GLA-SE Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (SE)</td>
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<tr>
<td>M. bovis</td>
<td>Phase 2A</td>
<td>Loss of &gt;100 genes within RD deletions</td>
<td>Epitopes in RD regions absent</td>
<td>ESAT-6</td>
<td>ESAT-6 Rv2660 Ag85B</td>
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<tr>
<td>M. bovis</td>
<td>Phase 2B</td>
<td>Same than BCG with urease C deletion and hly insertion</td>
<td>Epitopes in RD regions absent</td>
<td>Rv0125</td>
<td>Rv0125 Rv1196</td>
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<tr>
<td>M. vaccae</td>
<td>Phase 3</td>
<td>Heat</td>
<td>?</td>
<td>ESAT-6</td>
<td>ESAT-6 CFP-10 Ag85A</td>
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<td>M. indicus pranii</td>
<td>Phase 3</td>
<td>Heat</td>
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<td>?</td>
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<td>M. tuberculosis</td>
<td>Phase 2A</td>
<td>Detoxified fragments of M. tuberculosis in a liposomal formulation</td>
<td>?</td>
<td>ESAT-6</td>
<td>ESAT-6 Ag85A</td>
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*Slide courtesy Carlos Martin, Update on TB Vaccine Pipeline, Applied Sciences April 2020*
DIVERSITY OF CANDIDATES IN CLINICAL TRIALS

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<th>VIRAL VECTORED</th>
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<th>ADJUVANT/VIRAL VECTOR</th>
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<tr>
<td><strong>M. tuberculosis</strong></td>
<td>Phase 1</td>
<td>Adenovirus</td>
<td>Ag85A</td>
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<tr>
<td><strong>M. tuberculosis</strong></td>
<td>Phase 1</td>
<td>Chimpanzee Adenovirus + MVA</td>
<td>Ag85A</td>
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<td><strong>M. tuberculosis</strong></td>
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<td>Influenza virus</td>
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<td>Phase 2B</td>
<td>• AS01E Liposomal formulation of MPL and saponin QS-21</td>
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<td></td>
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<td>• IC31® antibacterial peptide and a synthetic oligonucleotide</td>
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