Testing new TB vaccines for people with HIV

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South African Tuberculosis Vaccine Initiative
University of Cape Town, South Africa
1. Candidate TB Vaccine Pipeline

2. TB Vaccine R & D Roadmap

3. WHO Preferred Product Characteristics

4. Age, Exposure, Infection and Disease – When to vaccinate against HIV-associated TB?

5. Testing candidate TB vaccines for infants and children

6. Testing candidate TB vaccines for adolescents and adults

7. Challenges & knowledge gaps
# CANDIDATE TB VACCINE PIPELINE

<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>Newborns</strong></td>
<td><strong>Adults and adolescents</strong></td>
<td><strong>Therapeutic</strong></td>
<td><strong>Therapeutic</strong></td>
</tr>
<tr>
<td>MTBVAC Biofabri / Univ. of Zaragoza / TBVI</td>
<td>MTBVAC Biofabri / Univ. of Zaragoza / TBVI / IAVI</td>
<td>ID93/GLASE IDRI/WT</td>
<td>ID93/GLASE IDRI/WT</td>
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<tr>
<td>ChadOx1.85™ MVA 85A</td>
<td>TB/Flu04L RIBSP</td>
<td>M72/ASO1E GSK, BMGF</td>
<td>VPM1002 SII, Max Planck, VPM, TBVI</td>
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<tr>
<td>McMaster, CanSino</td>
<td>Darvax</td>
<td>DAR-901 Dartmouth University, Aeras</td>
<td>MIP Cadila Pharma</td>
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<tr>
<td>GamTBVac MoH Russia</td>
<td>H56:IC31 SSI, IAVI</td>
<td>H56:IC31 SSI, IAVI</td>
<td>M. vaccae™ Anhui Zhifei Longcom</td>
</tr>
<tr>
<td><strong>Live attenuated</strong></td>
<td><strong>Viral vectored</strong></td>
<td><strong>Protein/adjuvant</strong></td>
<td><strong>Viral vectored</strong></td>
</tr>
<tr>
<td><strong>Whole cell inactivated</strong></td>
<td><strong>or fragmented mycobacteria</strong></td>
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</tbody>
</table>

**Courtesy Carlos Martin**

*Update on TB Vaccine Pipeline, Applied Sciences 2020*
WHO Preferred Product Characteristics (PPC)
Strategic Priority #1: New TB Vaccines for Use in Adolescents and Adults

• **OUTCOME MEASURE AND EFFICACY**
  – 50% or greater efficacy in preventing confirmed pulmonary TB
  – Protect both subjects with and without past *Mtb* infection
  – Protective in different geographical regions and latitudes

• **SAFETY**
  – Safety should be favourable in particular risk groups, such as individuals living with HIV/AIDS
WHO Preferred Product Characteristics (PPC)  
Strategic Priority #2:  
New TB Vaccines for Use in Neonates and Infants

• OUTCOME MEASURE AND EFFICACY
  – Equal to or greater than 80% vaccine efficacy as compared to baseline incidence  
  or superior efficacy as compared to BCG

• SAFETY
  – Improved safety as compared to current BCG
  – Demonstrated safety in HIV infected babies
  – Reduction of injection site swelling, pain, drainage, and scarring, and local lymphadenopathy  
  would represent welcomed improvement over BCG
Age, Exposure, Infection and Disease – When to vaccinate against TB?

Risk of *M. tuberculosis* exposure, infection & TB disease
Risk of *M. tuberculosis* exposure, infection & TB disease
Age, Exposure, Infection and Disease – When to vaccinate against HIV-associated TB?

### Mtb infection

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence Rate</th>
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<tr>
<td>Infants (0-1yr)</td>
<td>7%</td>
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<tr>
<td>Children (5-10yr)</td>
<td>28%</td>
</tr>
<tr>
<td>Adolescents (12-18yr)</td>
<td>50%</td>
</tr>
<tr>
<td>Adults (25yr)</td>
<td>75%</td>
</tr>
<tr>
<td>Adults (30yr)</td>
<td>88%</td>
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</tbody>
</table>

*Andrews LRM 2017*  
*Wood (TST) IJTLD 2010*  
*Mahomed IJTLD 2011*  
*Wood (TST) IJTLD 2010*

### TB Disease

2 TB incidence peaks <5 and 15-55 years of age

*Cape Town, South Africa*
High risk of progression to TB disease 1-2 years after *M.tb* infection (few people @ any time)

Low risk of progression to TB disease >2 years after *M.tb* infection (many people @ any time)
Pre-exposure Approach

Vaccinate before Mtb infection to prevent infection and/or TB disease

eg. Infant BCG replacement +/- heterologous boost for children, young adolescents
Post-exposure Approach

Vaccinate after Mtb infection to prevent TB disease

BCG → M.tb infection → TB disease

eg. subunit/killed vaccine in older adolescents and adults
Testing candidate TB vaccines for infants and children

<table>
<thead>
<tr>
<th>HIV</th>
<th>IGRA-</th>
<th>IGRA+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants</td>
<td>Adolescents</td>
</tr>
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</table>

Live mycobacterial vaccines
- BCG
- VPM1002
- MTBVAC

Subunit/killed vaccines
- M72/AS01E
- Others

Testing candidate TB vaccines for (older) adolescents and adults
Bacille Calmette Guerin (BCG)
Benchmark comparator live mycobacterial vaccines

BCG VACCINATION AGAINST TUBERCULOSIS IN CHICAGO
A Twenty-year Study Statistically Analyzed
Sol Roy Rosenthal, M.D., Ph.D., Erhard Loewinsohn, M.D., Mary L. Graham, M.D.,
Dorothy Liveright, Margaret G. Thorne, and Violet Johnson, with
Statistical Analysis by H. C. Batson, Ph.D.
Institution for Tuberculosis Research of the University of Illinois, the Chicago Municipal Tuberculosis
Sanitarium, Research Foundation, and the Cook County Hospital, Chicago

Controls

Vaccinated

Fig. 1. Comparison of time of development of tuberculosis in the vaccinated and control groups.
Each circle represents a case of nonfatal tuberculosis.

64% efficacy TBM
78% efficacy Disseminated TB

Colditz, Pediatrics 1995

Licensed multiple countries
UNICEF cost: 10-28 US cents per dose

Zwerling PLoS Medicine 2011
Study to Test the Efficacy and Safety of Recombinant BCG Vaccine in Prevention of TB Recurrence in India (vs placebo; 2,000 Rx cured TB patients)

Evaluation of Efficacy and Safety of VPM1002 in Comparison to BCG in Prevention of TB Infection in Infants (vs BCG; 6,940 newborn infants, incl. HEU)

Phase 3 POD trial VPM-1002 (vs MIP vs placebo; 12,000 household contacts >6 yr)

May be less reactogenic vs BCG in infants
Subcutaneous injection site abscess
n=5 (41%) BCG
n=4 (11%) VPM

Publication of infant Phase 2 data awaited...

ClinicalTrials.gov Identifier: NCT03152903
Recruitment Status: Recruiting
First Posted: May 15, 2017
Last Update Posted: February 28, 2018
See Contacts and Locations

ClinicalTrials.gov Identifier: NCT04351685
Recruitment Status: Not yet recruiting
First Posted: April 17, 2020
Last Update Posted: April 17, 2020
See Contacts and Locations
MTBVAC

Phase 2 infants
Phase 2 adults

Safety, immunogenicity, dose-escalation
18 BCG+ IGRA- adults, 36 BCG- infants
(3:1 MTBVAC vs BCG)
Well-tolerated
Dose-related IGRA conversion/reversion
Diagnosis unconfirmed TB (vs BCG/MTBVAC)

MTBVAC Study in Adults With and Without Latent Tuberculosis Infection in South Africa (2:1 vs BCG; n=144 IGRA+ IGRA-)

→ Phase 3 infant POD trial 2022 (incl. HEU)
BCG efficacy is variable
Average RR 0.5 (0.35 – 0.72)

BCG protects against TB disease in infants, and Mtb-uninfected children

No significant protection in Mtb-infected and uninfected adults
*Meta-analysis, Mangtani CID 2014*

Implications for efficacy of BCG and new live mycobacterial vaccines in high TB burden countries where >40% adolescents/adults are Mtb-infected

Risk of disseminated BCG disease in HIV-infected infants (ART-)
*Hesseling, Bulletin WHO 2009*
BCG vaccination protects against TB for +/- 10 years

Efficacy declines over time in most studies
Some exceptions
Few studies lasted >15 years
BCG Revaccination (or heterologous vaccine boost) in adolescence?

Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi

- No longer practiced in Eastern Europe
- 2 large RCT showed no efficacy of BCG revaccination
- TST/IGRA status unknown
- No efficacy of primary BCG in Karonga, Malawi (Ponnighaus Lancet 1992)
- 33% VE subgroup children <11 years of age in Salvador, Brazil

Can BCG Revaccination prevent TB in children who are Mtb-uninfected at vaccination?
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

N=1,800 IGRA-
Aged 10-18 yr
FU 48 months
Sustained IGRA+ conversion (QFT-Plus)

ClinicalTrials.gov Identifier: NCT04152161

Sufficient evidence POI to test efficacy against TB disease?
Take Home Messages #1

1. New live mycobacterial vaccines (VPM1002, MTBVAC) entering trials to replace BCG at birth include HEU infants

2. Some evidence suggests efficacy of BCG Revaccination against TB disease should be tested in IGRA- adolescents without HIV
   - Target population pre-teens?
   - Large, long, costly trial
   - Bridging studies – correlate of protection
   - Include other live mycobacterial vaccines (VPM1002, MTBVAC)

3. Inclusion of IGRA- adolescents with HIV (ART)
   - Justified on basis of 4X risk vs HIV-
   - Theoretical risk of disseminated vaccine disease
   - Would require safety and immunogenicity data
     - BCG, live mycobacterial vaccines

Testing candidate TB vaccines for infants and children

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Live mycobacterial vaccines
- BCG
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Subunit/killed vaccines
- M72/AS01E
- Others

Testing candidate TB vaccines for (older) adolescents and adults
**M. obuense**  
(SRL172)  
POD

**DarDar Trial (Tanzania)**

5-dose regimen *M. obuense (vaccae)* 1:1 Placebo  
2,013 PLWH  CD4 >200  TST+/- 2 → 28% ART  
FU median 3 years

Well-tolerated, no effect CD4/VL  
No efficacy Disseminated TB (#1 endpoint)  
39% efficacy Definite TB (#2 endpoint)
3,575 IGRA+ HIV- adults 18–50 years
Zambia, Kenya, SA

Randomized (1:1), M72/AS01E (M.tb proteins 32A and 39A) or Placebo, 2 doses, 1 month apart

VE 49.7% (95% CI 2.1 to 74.2)
Will M72/AS01\textsubscript{E} offer protection against TB in people who are IGRA- at vaccination?
Modelling studies

Assumptions: 10-year, 70% efficacy against disease

Vaccines with efficacy in IGRA+ populations $\rightarrow$ greatest reduction in TB incidence by 2050
(IRR 51%, 52%, and 54% in China, South Africa, India)

Vaccines with efficacy only in IGRA- populations $\rightarrow$ moderate reduction in TB incidence by 2050
(IRR 19, 36, and 51% in China, South Africa, India), with greater impact in higher-transmission settings.

"In South Africa, where HIV prevalence is high, contraindication in HIV-positive populations was found to substantially reduce the overall epidemiologic impact of TB vaccination."

Harris et al, Sci Transl Med 2020
Is M72/AS01<sub>E</sub> safe and immunogenic in people with HIV?

37 (22) HIV infected adults, Switzerland
Stable on ART, CD4 cell count >200/microL

M72/AS01 well tolerated
Polyfunctional M72-specific CD4+ T-cell response persisted through 210 days
All vaccinees seropositive for anti-M72 IgG after second vaccination to study end

240 (120) HIV uninfected and HIV infected adults, India
HIV infected cohort, ART-naïve and stable on ART

M72/AS01 well tolerated, no adverse effects on CD4 or VL
Polyfunctional M72-specific CD4+ T-cell responses and M72-specific IgG responses higher in ART-stable vs ART-naïve subjects

ClinicalTrials.gov Identifier: NCT04556981

**Recruitment Status**: Active, not recruiting
**First Posted**: September 21, 2020
**Last Update Posted**: December 22, 2020
Take Home Messages #2

1. Evidence that a killed/inactivated vaccine (*M. obuense*) offers protection against TB in people with HIV

2. Evidence of efficacy of a subunit vaccine (M72/AS01E) against TB in IGRA+ people without HIV
   - Efficacy in IGRA- unknown
   - Lower immunogenicity (cellular) in IGRA-

3. M72/AS01E appears safe in people with HIV
   - Small studies, more data needed
   - Lower immunogenicity (cellular, humoral) in ART-

4. Modelling suggests vaccination of IGRA+ populations --> greatest reduction in TB incidence by 2050
   - Impact of vaccination of IGRA- depends on transmission setting
Challenges

**Balance of risk and benefit**
Avoidance of risk to children and adults with HIV vs urgent need for protection against HIV-associated TB

**Enable inclusion in planned efficacy trials**
Test safety, immunogenicity of live attenuated mycobacterial vaccines (rBCG, Mtb) in infants, children and adolescents with HIV

**Mitigate risks**
Inclusion of ART-stable - excludes highest risk group for HIV-associated TB

**Knowledge Gaps**
Model impact of TB vaccination, ART and IPT coverage, against HIV-associated TB

Demonstrate cost-effectiveness in TB/HIV endemic countries → policy
Unknowns
Acknowledgements

040 Trial Investigators
018 Trial Investigators
BioFabri, MTBVAC team
SII, VPM1002 team
Carlos Martin, University of Zaragoza
Fordham von Reyn, Dartmouth College
Epi, Modelling and Trial Designs RC, CTVD
DAIDS Cross-network TB Vaccine Working Group
Johan Vekemans, WHO New TB Vaccine Working Group
Tom Scriba, Elisa Nemes, SATVI, University of Cape Town
EXTRA SLIDES
DIVERSITY OF CANDIDATES IN CLINICAL TRIALS

Phase 1
- M. tuberculosis
- Adenovirus
- Ag85A

Phase 2A
- M. tuberculosis
- Chimpanzee Adenovirus + MVA
- Ag85A

Phase 2B
- M. tuberculosis
- Influenza virus
- ESAT-6 Ag85A

Phase 3
- M. indicus prandi
- Non-Tuberculous Mycobacteria
- Heat

INACTIVATED
- M. vaccae
- Phase 3
- Non-Tuberculous Mycobacteria
- Heat

M. vaccae
- Non-Tuberculous Mycobacteria
- Heat

M. bovis
- Phase 2B
- Loss of >100 genes within RD deletions
- Epitopes in RD regions present

M. bovis
- Phase 3
- Same than BCG with urease C deletion and lysteriolysin insertion
- Epitopes in RD regions absent

M. tuberculosis
- Phase 2A
- Double deletion of phoP/adD25 virulence genes
- ALL present

SUBUNITS
- M. tuberculosis
- Phase 2B
- AS01E Liposomal formulation of MPL and saponin Q5-21
- IC31β antibacterial peptide and a synthetic diphosphonucleotide
- Rv0125 Rv1196

M. tuberculosis
- Phase 2A
- DEAE-dextran core and CpG dinucleotide
- ESAT-6 CFP10 Ag85A
- Rv3920 Rv3619 Rv2698 Rv1813

M. tuberculosis
- Phase 1
- GLA-SE Glucosynarosyl Lipid A (GLA), in oil-in-water emulsion (SE)

WHOLE CELL MYCOBACTERIA
- M. tuberculosis
- Phase 1
- M. vaccae
- Phase 3
- M. bovis
- Phase 2B
- M. bovis
- Phase 3
- M. tuberculosis
- Phase 2A

CONTENT IN M. tuberculosis T-CELL ANTIGENS
- Ag85A
- Non-Tuberculous Mycobacteria
- Heat

CONTENT IN M. tuberculosis T-CELL ANTIGENS
- M. vaccae
- Phase 3
- M. bovis
- Phase 2B
- M. bovis
- Phase 3
- M. tuberculosis
- Phase 2A

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

Courtesy Carlos Martin
Update on TB Vaccine Pipeline, Applied Sciences 2020
DIVERSITY OF THE PIPELINE OF TB VACCINE CANDIDATES IN CLINICAL TRIALS

**Update on TB Vaccine Pipeline**

**Table of Vaccine Candidates**

<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</td>
<td>Heat</td>
<td>Detoxified fragments of M. tuberculosis in a liposomal formulation</td>
<td>ALL present</td>
</tr>
<tr>
<td>M. bovis</td>
<td>Loss of &gt;100 genes within RD deletions</td>
<td>Epitopes in RD regions absent</td>
<td></td>
</tr>
<tr>
<td>Phase 2B</td>
<td>Same than BCG with urease C deletion and liquefying insertion</td>
<td>Epitopes in RD regions absent</td>
<td></td>
</tr>
<tr>
<td>Phase 2A</td>
<td>Double deletion of phiP-fadD26 virulence genes</td>
<td>ALL present</td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. vaccae</td>
<td>Heat</td>
<td></td>
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<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. iquins</td>
<td>Heat</td>
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<tr>
<td>Phase 3</td>
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<td>M. vaccae</td>
<td>Detoxified fragments of M. tuberculosis in a liposomal formulation</td>
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<td>Phase 2B</td>
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<tr>
<td>M. tuberculosis</td>
<td>Heat</td>
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<tr>
<td>Phase 1</td>
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<td>M. tuberculosis</td>
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<td>Phase 2A</td>
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<td>Phase 2B</td>
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</tbody>
</table>

**Adjuvants**

- GLA-SE: Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (SE)
- IC31β: Antibacterial peptide and a synthetic oligonucleotide
- AS01E: Liposomal formulation of MPL and saponin QS-21
- DEAE-dextran core and CpG oligonucleotide
- Adenovirus
- Chimpanzee Adenovirus +MVA
- Influenza virus

**References**

- Rv3820
- Rv3619
- Rv2806
- Rv1813
- ESAT-6
- Rv2660
- Ag85B
- Rv0128
- Rv1196
- ESAT-6
- CFP-10
- Ag85A
- Ag85A
- Ag85A
- Ag85A