Tuberculosis

New Generation Vaccines

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# The End TB Strategy at a glance

<table>
<thead>
<tr>
<th>VISION</th>
<th>A WORLD FREE OF TB — zero deaths, disease and suffering due to TB</th>
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<tbody>
<tr>
<td>GOAL</td>
<td>END THE GLOBAL TB EPIDEMIC</td>
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## INDICATORS

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Milestones</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)</td>
<td>35%</td>
<td>75%</td>
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<tr>
<td>Percentage reduction in the TB incidence rate (compared with 2015 baseline)</td>
<td>20%</td>
<td>50%</td>
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<tr>
<td>Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown)</td>
<td>0%</td>
<td>0%</td>
</tr>
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## Top causes of death worldwide in 2015

- Ischaemic heart disease
- Stroke
- Lower respiratory infections
- Chronic obstructive pulmonary disease
- Trachea, bronchi, lung cancers
- Diabetess mellitides
- Alzheimer disease and other dementia
- Diarrhoeal diseases
- Tuberculosis
- Road injury

*Deaths from TB among HIV-positive people are shown in grey.*

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## World Health Organization
• TB vaccine pipeline update

• Preferred Product Characteristics (New TB Vaccine WHO Working Group)

• Non-human primate data

• Proof of concept trials (recent results)

• Pending results and new trials

• Future priorities and questions
Global Clinical Pipeline

Phase 1
- Ad5 Ag85A
  McMaster, CanSino
- ChAdOx185A/MVA85A (ID/IM/Aerosol)
  U. Oxford

Phase 2a
- RUTI
  Archivel Farma, S.L
- H4: IC31
  Sanofi Pasteur, SSI, Aeras
- MTBVAC
  Biofabri, TBV, Zaragoza, Aeras
- ID93 + GLA-SE
  IDRI, Wellicome Trust
- TB/FLU-04L
  RIBSP
- BCG Revaccination

Phase 2b
- DAR-901
  Dartmouth, GHIT
- M72 + AS01E
  GSK, Aeras
- H56: IC31
  SSI, Valneva, Aeras

Phase 3
- Vaccae™
  Anhui Zhifei Longoom
- VPM 1002
  SII, Max Planck, VPM, TBVI (Phase 2/3)
- MIP
  Cadila, ICMR

Viral Vector
Protein / Adjuvant
Mycobacterial – Killed, Whole Cell or Extract
Mycobacterial – Live

Revised on 3/28/18
Please note: Information is self-reported by vaccine sponsors

Courtesy Aeras, accessed 23 June 2018
• TB vaccine pipeline update

• **Preferred Product Characteristics**  
  *(New TB Vaccine WHO Working Group)*

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Strategic Priority #1
PPC: New TB Vaccines for Use in Adolescents and Adults

• **INDICATION**
  – Immunization for prevention of active pulmonary TB disease

• **TARGET POPULATION**
  – Adolescents and adults. Proof of concept should prompt pediatric studies.

• **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

*Courtesy Johan Vekemans; New TB Vaccine WHO Working Group*
Impact of adult vs infant vaccination strategies

Adult vaccine strategy 40% VE and 5-year protection (E) greater impact on TB incidence than infant vaccine 80% VE and lifelong protection (D) by 2050

Adult vaccine likely to prevent more infant TB cases than an infant vaccine
– due to reduction in M.tb transmission

Modeled impact of a new TB vaccine targeted at infants (D) or adults (E)

Knight, PNAS 2014

*waves = mass campaigns
Strategic Priority #2
PPC: New TB Vaccines for Use in Neonates and Infants

- **INDICATION**
  - Prevention of TB, including severe, disseminated, meningitis and pulmonary TB, in infants and young children

- **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

*Courtesy Johan Vekemans; New TB Vaccine WHO Working Group*
PPC: New TB Vaccines

• **DURATION OF PROTECTION**
  – Demonstrated efficacy ≥2 years for initial policy decision
  – ≥10 year protection after primary immunization

• **IMMUNOGENICITY**
  – Identification of a vaccine-induced immune correlate of protection
  – Conservation of biological specimens for future use

• **SCHEDULE**
  – ≤ 3 doses for primary immunization.
  – Booster dose(s) ≤ 5-10 years
  – Heterologous prime boost regimens after neonatal BCG considered

• **CO-ADMINISTRATION**
  – Favourable safety and immunologic non-interference

*Courtesy Johan Vekemans; New TB Vaccine WHO Working Group*
• TB vaccine pipeline update

• Preferred Product Characteristics
  (New TB Vaccine WHO Working Group)

• **Non-human primate data**

• Proof of concept trials (recent results)

• Pending results and new trials

• Future priorities and questions
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameria*, Mark Hetherington, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shao, J Bruce McClain, Gregory D Hossuy, Willem A Hanekom, Hassan Mahomed, Helan McShane, and the MVA85A 020 Trial Study Team

Source: Bill & Melinda Gates Foundation
RhCMV vaccination reduced extent of TB disease by 68% vs unvaccinated controls
14 of 34 (41%) showed no TB disease by CT or at necropsy vs 0 of 17 unvaccinated controls
10 Mtb-culture-negative for all tissues

Potential challenges for entry into clinical trials

Safety in humans
Manufacture
Alternative Routes BCG Administration

Intravenous high-dose BCG

Rhesus macaques, 6 per group

ID 2-8 x 10⁵ cfu/mL BCG

IV 2-8 X 10⁶ cfu/mL BCG

IT 2-8 X 10⁷ cfu/mL BCG

Aerosol nebulized HD *M. tuberculosis* challenge

High dose IV BCG

→ Improved lung/total pathology scores
→ Improved survival

Vs unvaccinated controls and ID BCG

Implementation and safety challenges

Research tool or viable strategy?
• TB vaccine pipeline update

• Preferred Product Characteristics (New TB Vaccine WHO Working Group)

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• **Proof of concept trials**
  – Prevention of *M. tuberculosis* infection (POI)
  – Prevention of Recurrent TB (POR)

• Pending results and new trials

• Future priorities and questions
Rationale for Prevention of Infection (POI) trials

Case-Control Studies
Evidence that primary BCG vaccination provides modest protection against M.tb infection (IGRA conversion)

Meta-analysis of 14 retrospective case-control studies (n=3,855)
BCG protective
RR for MTB infection 0.81 (95% CI 0.71 - 0.92)

Roy BMJ 2014

Mtb infection occurs >10x rate TB disease
Smaller, less costly proof of concept POI efficacy trials
Opportunity to discover immune correlates of protection
Long-term impact on TB disease (POD)?
Randomized controlled trial to evaluate safety, immunogenicity, and prevention of initial and/or sustained QuantiFERON-TB Gold In-tube (QFT) conversion by H4:IC31 or BCG revaccination

n=990 healthy, HIV-uninfected, QFT-negative, SA adolescents (12-17 years)
   BCG vaccinated in infancy
   No previous TB disease or household TB contact

3 arms, randomized 1:1:1
Double-blind intramuscular injection (D0 and D56) saline placebo OR H4:IC31® OR
Open-label intradermal injection (D0) BCG Vaccine (Statens Serum Institut) (2-8 x 10^5 CFU)

H4 (Sanofi Pasteur) subunit vaccine (mycobacterial antigens Ag85B, TB10.4) (not in QFT)
   Ag85B: expressed by both M.tb and BCG, mycolyl transferase
   TB10.4: expressed by both M.tb and BCG, secreted protein (same family as ESAT-6)

Follow-up 2 years: serial 6-monthly QFT testing (QFT tests antigens ESAT-6/CFP-10/TB-7.7)

   Primary endpoint: initial QFT conversion negative $\rightarrow$ positive
   Secondary endpoint: sustained QFT conversion negative $\rightarrow$ positive (6m)
Placebo  
n=49/310  
(16%)

H4:IC31  
n=44/308  
(14%)

BCG  
n=41/312  
(13%)

**Efficacy Primary Endpoint**

**QFT conversion (n=134; 14%)**

VE: 9.4%  20.1%

80% CI  
95% CI

**Time to QFT conversion (Months)**

At Risk

310  301  283  261  120
308  281  265  120
312  294  276  134
QFT Reversion (n=47; 37%)

Placebo 12/48 (25.0%)

H4:IC31 17/42 (40.5%)

BCG 18/39 (46.2%)
Efficacy Secondary Endpoint: Sustained QFT conversion (n=82; 63%)

Placebo  

H4:IC31  

BCG  

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>36/310</td>
<td>11.6%</td>
</tr>
<tr>
<td>H4:IC31</td>
<td>25/308</td>
<td>8.1%</td>
</tr>
<tr>
<td>BCG</td>
<td>21/312</td>
<td>6.7%</td>
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VE: 30.5% 45.4%
Impact of POI Trial results

1) *Evidence POI design can detect vaccine efficacy in high M.tb transmission setting*
   - identified *sustained* QFT conversion as suitable endpoint
   - POI needs validation as tool for vaccine up-selection in future POD trial

2) *Modest H4:IC31 signal, suggests biological effect*
   - first indication of protection against *M.tb* in humans by novel subunit vaccine

3) *Convincing BCG revaccination efficacy signal*
   - allow search for immune correlates of protection (*M.tb* infection)
   - justifies (re)evaluation of BCG revaccination for POD in *M.tb*-uninfected persons
DAR-901 TB Booster Vaccine to Prevent TB in Adolescents (DAR-PIA)

Vaccine: 3-dose ID DAR901 (inactivated whole cell *M. obuense*)
Sponsor: Dartmouth
Population: n=650 IGRA- adolescents
Endpoints: IGRA conversion
Site/s: Tanzania
A Phase 2, Double-blind, Randomized, Placebo-Controlled Study to Evaluate Prevention of Recurrence (POR)

Vaccine: 2-dose IM H56:IC31 (fusion protein Ag85B; ESAT-6 and Rv2660c)
Sponsor: Sponsor Aeras (SSI)
Population: 900 Rx cured TB patients
Endpoints: TB recurrence (confirmed) 12 months
Site/s: South Africa, Tanzania

PENDING:
POI - Adolescents
Phase 2a ID93 + GLA-SE Vaccine Trial in TB Patients After Treatment Completion

**Vaccine**  
2-dose IM ID93 + GLA-SE (fusion protein virulence Rv2608, Rv3619, Rv3620; & latency Rv1813 antigens)

**Sponsor**  
IDRI

**Population**  
N=60 Rx cured TB patients

**Endpoints**  
Safety and immunogenicity

**Site/s**  
South Africa
Study to Check the Efficacy and Safety of Recombinant BCG Vaccine in Prevention of TB Recurrence in India

Vaccine: single-dose ID VPM1002 (live recombinant BCG)
Sponsor: SII
Population: 2,000 Rx cured TB patients
Endpoints: Safety & TB recurrence (12 months)
Site/s: India

PENDING:
- POD – Household contacts (+MIP)
- POD -- Infants
Challenges for live mycobacterial vaccines

BCG efficacy is variable
Average RR 0.5 (0.35 – 0.72)

Highest BCG protection against TB disease in infants, and Mtb-uninfected children (RR 0.26), compared to Mtb-infected and -uninfected adults (RR 0.88)

Implications for efficacy of new live mycobacterial vaccines in high TB burden countries where >40% adults are Mtb-infected (Mtb-exposed/household contact designs; POR)

*Meta-analysis, Mangtani CID 2014*
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MTBVAC

Phase 1 infants

Dose-escalation Safety and Immunogenicity Study to Compare MTBVAC to BCG in Newborns With a Safety Arm in Adults

Vaccine
Single dose ID MTBVAC (live attenuated Mtb)

Sponsor
Biofabri

Population
18 BCG+ adults
36 BCG- infants

Endpoints
Safety, immunogenicity

Site/s
South Africa

ClinicalTrials.gov Identifier: NCT02729571

Recruitment Status: Completed
First Posted: April 6, 2016
Last Update Posted: May 1, 2018

Pending
Phase 2a SA infants
Phase 2a SA adults
Potential interference with diagnostic tests for M.tb infection

BCG → False+ tuberculin skin test (TST)
IGRA tests Mtb antigens ESAT-6/CFP-10/TB-7.7 (not present in BCG)

Vaccines containing ESAT-6 (eg. H56:IC31) and CFP-10 (eg. MTBVAC) may affect IGRA readout
  Frequency, magnitude, duration?
  Vaccine development vs test development

Challenge for implementation in populations where test for Mtb infection is indication for preventive therapy eg. Children (NCT02729571)

Early post-vaccination IGRA
ESAT-6-free IGRA
CFP-10-free IGRA
WBA peptide pool
Phase III Clinical Study of Efficacy and Safety of Vaccae™ to Prevent Tuberculosis

Vaccine  6-dose IM *M. vaccae* (inactivated whole cell)
Sponsor  Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.
Population 10,000 Mtb infected (TST+) adults
Endpoints  TB disease
Site/s  China

Results awaited...
Study to Evaluate the Efficacy of GlaxoSmithKline (GSK) Biologicals' Candidate Tuberculosis (TB) Vaccine in Adults

Vaccine: 2-dose IM M72/ASO1\textsubscript{E} (fusion protein Mtb32A, Mtb39A)
Sponsor: GSK (Aeras)
Population: 3,500 IGRA+ adults
Endpoints: Incident TB disease (confirmed), 36 months
Site/s: South Africa, Kenya, Zambia

Results awaited September 2018
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Strategies for Protection of M.tb-infected and M.tb–uninfected Populations

Estimated 23% global population M.tb-infected

High TB incidence countries >40%

Houben, PloS Medicine 2016

TB disease incidence rises rapidly from adolescence

Mahomed IJTL 2011
Wood SAMJ 2010

Implications for optimal age of vaccination/s
Strategies for Protection of M.tb-infected and M.tb–uninfected Populations

BCG revaccination POI efficacy signal requires validation in POD trial among Mtb-uninfected populations (77%)
- durability
- high vs low TB transmission/M.tb infection prevalence
- geography/genetic background

→ Target population younger adolescents?

Pending results from POD efficacy trials among Mtb-infected populations (23%)

→ Target population older adolescents/adults?

Key strategy questions:
- Optimal age of vaccination/s?
- Single vaccine?
- Homologous prime and boost?
- Heterologous prime and boost?
Changes in TB vaccine R & D stakeholder landscape

Funding commitment to new TB vaccine development by European & Developing Country Clinical Trials Partnership (EDCTP) – 2017


UN General Assembly High-level Meeting on Ending TB – 2018

Establishment of Gates Medical Research Institute – 2018

Limited global capacity for large TB vaccine efficacy trials

Organizational/ operational and trial site capacity

Lack of business incentive for late stage development

Dependent on small group of non-industry funders

Need to widen funding acess