Progress in TB Vaccine Development

Michele Tameris

South African Tuberculosis Vaccine Initiative (SATVI)
University of Cape Town, South Africa
BCG and the need for a new TB vaccine

Prevention of TB Disease - Infants
- Adolescents & Adults

Prevention of MTB Infection - Infants
- Adolescents & Adults

Challenges and opportunities for testing new TB vaccines
HOW TO PREVENT CONSUMPTION (TUBERCULOSIS) AND OTHER GERM DISEASES

For School Children to Take Home and to Read Every Day.

DON'T FORGET THESE FACTS.

Germs are very small microscopic plants. Germs are found in all Dust and Dirt. Some germs are harmless, others cause disease. Germs cause Consumption. Avoid germs and Prevent Consumption.

TRY TO

TRY to breathe through the nose rather than through the mouth.
TRY to fill the lungs with pure air, free from dust.
TRY to turn the head away from a person when coughing or sneezing, or hold a handkerchief or your hand over your mouth.
TRY to spit out material coughed up from the lungs.
TRY to spit into a piece of paper or cloth and burn as soon as possible.
TRY to gargle your throat with salt water or some other mild mouth wash after being exposed to any contagious disease.
TRY to clean the nose with a handkerchief.
TRY to keep the hands clean.
TRY to keep your finger nails cut short.
TRY to brush your teeth night and morning.
TRY to eat clean food and drink pure water.
TRY to eat slowly and chew your food well.
TRY to keep moving about when heated from play.
TRY to keep your feet dry.
TRY to sleep in a room with partly-opened windows.
TRY to live in the sunshine.
TRY to be out of doors as much as possible.

TRY NOT TO

Try NOT to take a full breath in a cloud of dust.
Try NOT to cough or sneeze in another’s face.
Try NOT to swallow what you raise in coughing.
Try NOT to spit upon the floor or sidewalk.
Try NOT to cough long without seeing a physician.
Try NOT to kiss a sick friend.
Try NOT to pick your nose with your fingers.
Try NOT to eat with dirty hands.
Try NOT to eat things made dirty by the handling of other persons.
Try NOT to eat a piece of candy or apple picked up from the sidewalk or street.
Try NOT to have long and dirty finger nails.
Try NOT to go about with unclean teeth.
Try NOT to drink out of a cup that has been used unless you wash it first.
Try NOT to eat when heated or tired.
Try NOT to eat fast.
Try NOT, when heated, to sit down where it is cold.
Try NOT to play in wet shoes and stockings.
Try NOT to sleep in a warm or hot room.
Try NOT to shut out the sunshine.
Try NOT to form the habit of living around a stove.

Gardner Association for the Prevention and Relief of Tuberculosis.
Robert Koch’s “therapeutic vaccine”
Purified Tuberculin Protein (PPD)

August 1890

• 10th International Medical Congress in Berlin attended by 8000 participants
• Keynote speech by Koch on opening day
• Urged by Emperor William II to present something spectacular

Guinea pigs, which are known to be highly susceptible to tuberculosis, no longer respond to infection with tubercle bacilli once they had been pretreated with such substances. Moreover, in guinea pigs that suffered from severe tuberculosis, the disease process could be brought to an end without harming the animals. I do not want to draw further conclusions from these experiments, but only to state that the possibility exists to inactivate pathogens in the host without major side effects—a possibility that was thus far considered extremely unlikely.

The substance with which the new treatment against tuberculosis is being performed, is a glycerol extract of pure culture of tubercle bacilli.

• General acclaim. Patients and scientists flocked to Berlin....
Robert Koch’s ‘cure’ for TB: Purified Tuberculin Protein (PPD)

1891: First negative reports of clinical trials
- Total 1769 patients
- More patients died during therapy than were cured
- Most of deaths due to advanced pulmonary TB
- Fewer that 20% of all patients improved substantially
- 50% showed no improvement

Animal models may be misleading....
The Doctor, The Vet, and The Cow

**Bacille Calmette-Guerin (BCG) Vaccine**

- Albert Calmette (physician) and Camille Guerin (vet)
- Pasteur Institute, Lille, France (1921)
- Attenuated bovine TB strain (*Mycobacterium bovis*)
- Cultured virulent bacilli obtained from a cow with TB mastitis
- Added bile as natural culture detergent → organism unexpectedly lost virulence

- Tested as vaccine in calves, guinea pigs, rabbits, horses, monkeys
Natural Experiments with BCG Vaccination

Table 1  Tuberculosis Case and Death Rates Among Student Nurses at Ullevål Hospital, Norway, by Tuberculin and BCG Vaccination on Entry, 1927–1946

<table>
<thead>
<tr>
<th>Tuberculin and Vaccination Status on Entry</th>
<th>No.</th>
<th>Person-years of Observation</th>
<th>Rate/1000 Person-years</th>
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<tbody>
<tr>
<td>Tuberculin-positive, not vaccinated</td>
<td>668</td>
<td>1772</td>
<td>12.4</td>
</tr>
<tr>
<td>Tuberculin-negative, not vaccinated</td>
<td>284</td>
<td>687</td>
<td>141.2</td>
</tr>
<tr>
<td>Tuberculin-negative, vaccinated</td>
<td>501</td>
<td>1450</td>
<td>24.1</td>
</tr>
</tbody>
</table>

BCG vaccination associated with 7-fold reduction in TB disease and TB mortality

*Heimbeck & Scheel, Bjartveit IJTLD 2003*
Fig. 1. Comparison of time of development of tuberculosis in the vaccinated and control groups. Each circle represents a case of nonfatal tuberculosis.

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. Baison, Ph.D.

Institution for Tuberculosis Research of the University of Illinois, the Chicago Municipal Tuberculosis Sanitarium, Research Foundation, and the Cook County Hospital, Chicago
BCG offers partial protection against TB disease in children

74% efficacy against all forms*

64% efficacy against TBM

78% efficacy against disseminated disease

*Data from BCG efficacy trials published 1949-1961
The BCG Atlas

Zwerling PLoS Medicine 2011
Tuberculosis Cases

In 2003 tuberculosis, often abbreviated to ‘TB’, affected 8.7 million people. Most of these people lived in Asia and Africa, a small proportion were in Europe and the Americas.

The World Health Organisation reports that someone with open tuberculosis would infect 10 to 15 people a year. So when a certain number of people are infected it is very hard to stop it spreading further. Tuberculosis bacilli are spread through the air when someone sneezes or coughs.

In the past 50 years drugs have been developed to treat tuberculosis. The disease has since developed strains that are resistant to those drugs.

Territory size shows the proportion of worldwide tuberculosis cases found there.

“\textit{I would like to invite all of us to re-affirm our commitment to Stop TB, and thereby gift our children a tuberculosis-free world.}”

Samlee Plianbangchang, 2004
TB Vaccine Development Challenges

Murine model does not mimic human pulmonary TB disease
Limited access to NHP model

Lack of immune correlate of protection
Role of CD4 T cell IFN-gamma response?
Role of highly conserved T cell epitopes?

Vaccine candidate setbacks
Cost and duration of efficacy trials

Can MTB infected adults in TB endemic countries be protected?
Global Clinical Pipeline of TB Vaccine Candidates

- **Prevention of infection**
- **prevention of recurrence**
- **intranasal**
TB Incidence is Age-dependent

Persistently high rates of TB disease in BCG-vaccinated individuals

Bimodal peaks in TB disease incidence ages 0-5 and 20-25 years

Mahomed IJTLD 2011

Young children have higher risk of progression from TB infection to disease and higher risk of disseminated disease (TB meningitis and miliary TB)

Figure 1 All tuberculosis incidence rate by age (years) in Cape Town, July 2002–June 2003 (n = 5039). Source: City Health Directorate of the City of Cape Town (notified TB cases) and Census 2001 (population estimates).
Prevention of Disease (POD) in Infants

BCG and/or new vaccine → TB Infection → TB Disease

MTB Exposure

Durable Protection

Pre-exposure Strategy (IGRA-/TST-)

Newborn infants are truly MTB unexposed and MTB uninfected
The first infant TB vaccine efficacy trial since BCG....

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

Michele D Tameris*, Mark Hathorn*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hossey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 620 Trial Study Team

MVA85A vaccination at 4-6 months of age provided no additional protection against TB disease (strict primary endpoint definition) in infants who had already received BCG vaccination at birth

Childhood TB pauci-bacillary

Sample collection ‘difficult’

Microbiological confirmation in half of primary endpoint cases and 11% of all children treated for TB

Tameris, Lancet 2013
Rationale for Adult TB Vaccine Strategy

Adults are responsible for MTB transmission

Prevention of adult pulmonary TB disease would have the greatest short- to medium-term impact on TB control

Image courtesy of Burdens of Africa
Rationale for Adult TB Vaccine Strategy

Right Panel E
Adult vaccine strategy
40% VE, 5-year protection
greater impact on TB incidence than...

Left Panel D
Infant vaccine strategy
80% VE and lifelong protection

Adult vaccine likely to prevent more infant TB cases than an infant vaccine, due to reduction in transmission

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

*Assumes VE in MTB infected adults; serial mass campaigns; note equivalence by 2050

Knight, PNAS 2014
Prevention of Disease (POD) in Adults

BCG at birth → TB Infection → New Vaccine → TB Disease

MTB Exposure → Durable Protection

Post-exposure Strategy (IGRA+/TST+)

Can MTB infected people be protected?
Block replication of live mycobacterial vaccines?
Mask additional vaccine effect (<BCG <MTB)?
Risks for post-exposure POD vaccination strategies

BCG protective efficacy is variable

Greatest in infants and MTB uninfected children (RR 0.26)

Lowest in MTB infected and uninfected adults (RR 0.88)

\(\rightarrow\) MTB infected adults may be the most difficult population to provide additional protection (particularly with live mycobacterial vaccines like BCG)

Meta-analysis, Mangtani CID 2014
Long-standing MTB infection offers some protection against TB disease

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Incidence Rate Ratio [95% CI]</th>
</tr>
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<tbody>
<tr>
<td>Geer 1934</td>
<td>0.21 [0.02 – 2.03]</td>
</tr>
<tr>
<td>Geer 1934</td>
<td>0.04 [0.03 – 0.04]</td>
</tr>
<tr>
<td>Heimbeck 1938</td>
<td>0.58 [0.33 – 1.02]</td>
</tr>
<tr>
<td>Heimbeck 1938</td>
<td>0.22 [0.10 – 0.50]</td>
</tr>
<tr>
<td>Heimbeck 1938</td>
<td>0.12 [0.08 – 0.17]</td>
</tr>
<tr>
<td>Myers 1940</td>
<td>0.59 [0.26 – 1.33]</td>
</tr>
<tr>
<td>Myers 1941</td>
<td>0.25 [0.05 – 1.32]</td>
</tr>
<tr>
<td>Hastings 1941</td>
<td>0.15 [0.02 – 1.41]</td>
</tr>
<tr>
<td>Brahdy 1941</td>
<td>0.08 [0.03 – 0.23]</td>
</tr>
<tr>
<td>Israel 1941</td>
<td>0.51 [0.27 – 0.94]</td>
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<td>Wright 1941</td>
<td>0.04 [0.03 – 0.04]</td>
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<td>Schwartz 1942</td>
<td>0.16 [0.02 – 1.09]</td>
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<td>Daniels 1944</td>
<td>0.18 [0.12 – 0.29]</td>
</tr>
<tr>
<td>Lim–Yuen 1946</td>
<td>0.21 [0.05 – 0.85]</td>
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<tr>
<td>Madsen 1942</td>
<td>0.13 [0.08 – 0.22]</td>
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<tr>
<td>Madsen 1942</td>
<td>0.19 [0.08 – 0.45]</td>
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<tr>
<td>Holm 1946</td>
<td>0.47 [0.13 – 1.66]</td>
</tr>
<tr>
<td>Thompson 1949</td>
<td>0.42 [0.18 – 0.98]</td>
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<tr>
<td>Badger 1949</td>
<td>0.57 [0.34 – 0.95]</td>
</tr>
<tr>
<td>Dickie 1950</td>
<td>0.23 [0.08 – 0.70]</td>
</tr>
<tr>
<td>Dickie 1950</td>
<td>0.23 [0.03 – 1.87]</td>
</tr>
<tr>
<td>Poole 1954</td>
<td>0.32 [0.15 – 0.69]</td>
</tr>
<tr>
<td>Karns 1959</td>
<td>0.41 [0.11 – 1.50]</td>
</tr>
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</table>

Random Effects Model

Individuals with latent MTB infection have 79% lower risk of developing TB disease after reinfection than uninfected individuals

Andrews CID 2012

Potential masking of vaccine effect in high burden settings with repeated MTB exposure
Recent MTB infection associated with highest risk of disease

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TST- to TST+ conversion (100%) associated with 12-fold greater TB incidence than baseline TST+ in BCG naïve individuals

Heimbeck & Scheel, Bjartveit IJTLD 2003
Recent MTB infection associated with highest risk of disease

6,000 BCG vaccinated South African adolescents (50% IGRA+ at baseline)

TB Incidence (2 year follow-up)

<table>
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<th>Status</th>
<th>Rate (per 100 person years)</th>
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<tr>
<td>IGRA-</td>
<td>0.22</td>
</tr>
<tr>
<td>IGRA+</td>
<td>0.64</td>
</tr>
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Rate of TB disease in MTB infected is 3-fold that of uninfected people

<table>
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<th>Transition</th>
<th>Rate (per 100 person-years)</th>
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<tr>
<td>IGRA- → IGRA-</td>
<td>0.17</td>
</tr>
<tr>
<td>IGRA- → IGRA+</td>
<td>1.46 (0.82–2.39)</td>
</tr>
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Rate of TB disease in MTB uninfected who become infected is 8-fold that of uninfected people, and twice that of previously MTB infected people

Mahomed PLoS ONE 2011
Machingaidze AJRCCM 2012
Can a TB vaccine protect against MTB infection?

Natural Experiments

n=953 (81% BCG-vaccinated; 29% IGRA+)
BCG vaccinated 23% IGRA+
Unvaccinated 57% IGRA+
OR 0.52 (95% CI 0.32 to 0.85) → BCG vaccine effectiveness against MTB infection 20%.

Michelson Thorax 2014
The rationale for a Prevention of Infection (POI) vaccine

**Case-Control Studies**
Evidence that BCG vaccination provides (modest) protection against IGRA conversion

Meta-analysis of 14 retrospective case-control studies (n=3,855)

BCG protective
**RR (MTB infection) 0.81**
(95%CI 0.71-0.92)

*Roy BMJ 2014*

Note: Primary BCG vaccination, not BCG revaccination
Prevention of Infection (POI) in Adolescents & Adults

BCG at birth

New Vaccine

TB Infection

TB Disease

Durable Protection

MTB Exposure

Pre-exposure Strategy (IGRA-/TST-)

*Adolescents and young adults in TB endemic countries will have been exposed to BCG vaccine and non-tuberculous mycobacteria
The rationale for a Prevention of Infection (POI) vaccine

Surely, if we can prevent MTB infection, we prevent TB disease?

90% of MTB infected individuals will never progress to TB disease in their lifetime

An effective POI vaccine that prevented MTB infection only in these people would have little impact on transmission

An ineffective POI vaccine that did not prevent MTB infection might still be effective in preventing progression to TB disease and would have impact on transmission

Ideally prevent MTB infection in the 10% who would progress to TB disease
Benefit maximal infants, adolescents & young adults (before MTB exposure)
Likely to be a long-term strategy
Testing POI vaccine strategies

**PROS**
- Rate of IGRA conversion 10 x TB disease (SA)
- Objective, high incidence endpoint
- Highly efficient ‘experimental medicine’ design
- Signal accelerated development into POD efficacy trials

**CONS**
- IGRA not gold standard test for MTB infection
- Spontaneous IGRA reversion is common
- POI strategy excludes subunit and MTB vaccines containing/secretrying ESAT-6
- Limited to children, adolescents, young adults
- 50-80% of individuals in TB endemic countries MTB infected in high school

**ClinicalTrials.gov NCT02075203**

Evaluate safety, immunogenicity, and prevention of infection by BCG revaccination, or by the novel vaccine H4:IC31 (AERAS-404), compared to placebo, in 990 SA adolescents.
Testing POD vaccines in MTB uninfected persons
Pre-exposure Strategy

**PROS**
Highest likelihood of observing POD vaccine efficacy?

**CONS**
Limited to children, adolescents, young adults
50-80% of individuals in TB endemic countries MTB infected in high school

Needs to be at least safe in IGRA+ persons
Avoid a strategy that requires pre-vaccination IGRA testing

Modest short-term impact on MTB transmission
Vaccination of IGRA- → long-term public health impact
TB endpoint accrual affects vaccine efficacy trial size, duration

High TB incidence rates make POD trials in MTB infected adults cost-effective, but this population may be the most difficult in which to demonstrate vaccine efficacy.

Low TB incidence in MTB uninfected adults would make pre-exposure POD trials larger and longer than equivalent trials in infants.

Adults (SA)
*Extrapolated from average adult rate compared to adolescents in same study region (980 vs 450 per 100 py)

Machingaidze AJRCCM 2012; Mahomed, PloS ONE 2011
In 4 years our only licensed TB vaccine, BCG, will be 100 years old...