Big Picture Scientific Challenges in Developing New TB Vaccines

Sara Suliman, MPH, PhD
Assistant Professor
Thursday, April 13th, 2023

TB Vaccine Development: The Next Chapter Starts Now
FIG. 12
Estimated TB incidence in 2021, for countries with at least 100 000 incident cases
The countries that rank first to eighth in terms of numbers of cases, and that accounted for about two thirds of global cases in 2021, are labelled.
Post COVID-19 uptick in TB-related mortality

FIG. 6
Global trends in the estimated number of TB deaths (left) and the mortality rate (right), 2000–2021

The horizontal dashed line shows the 2020 milestone of the End TB Strategy, which was a 35% reduction in the total number of TB deaths between 2015 and 2020. Shaded areas represent 95% uncertainty intervals.

Success in HIV-positive people largely attributed to advancements in antiretroviral treatments
Key transition stages in TB: vaccination opportunities

Exposure

Diagnosis

Progression 5-10%

M.tbc infection Active TB TB treatment

Cure

Re-exposure

Re-infection TB

Relapse/Recurrence

Different endpoints in TB vaccine trials:
1. Prevention of infection (POI)
2. Prevention of disease (POD)
3. Prevention of recurrence (POR)

Adapted from Thomas Scriba, University of Cape Town
Review of Vaccine Clinical Trial Stages

**FIGURE 1** | Flowchart showing traditional process of vaccine development from exploratory, pre-clinical studies to Phase 1 studies in a comparatively few control volunteers as depicted by the figure to larger Phase 2 and Phase 3 studies. The symbol is a representation of the number of human subjects in trials.

Timelines are generally longer for TB vaccine trials!

Reference: PMID: 33163000 (2020)
What do we know about the efficacy of BCG?

Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis


> 100 years old!

Reference: PMID: 35961354 (2022)
TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 15 vaccine candidates in the pipeline as of October 2022, of which nine are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

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

Trial status
- Active trials
- No active trials

Candidate 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 candidate indication
- POI: Prevention of Infection
- POD: Prevention of Disease
- POR: Prevention of Recurrence
- Thp: Therapeutic

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.newtbvaccines.org/tb-vaccine-pipeline/](http://www.newtbvaccines.org/tb-vaccine-pipeline/)

Last update: 02 November 2022
Selection of antigens and adjuvants to include in the vaccine

- *Mycobacterium tuberculosis* has ~ 4000 genes, variably expressed in different lineages and disease states
- Which adjuvants can help stabilize a long-term memory response with minimal side effects?
- Promise of mRNA vaccines? New “adjuvant” effects?
Selection of Populations

Infants:
- Surpassing BCG
- Paucibacillary TB
- Maternal health status

Adults/adolescents:
- BCG ‘revac’ or surpassing BCG
- Clinical endpoints
- Transmission chains

Elderly or immunocompromised:
- Immunogenicity?
- Comorbidities
- Transmission chain (and myths)

We cannot assume that protection in one population can be generalizable to other populations.
A shift in focus from infants to adolescents and adults

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


Reference: PMID: 23391465 (2013)

Figure 3: Cumulative incidence of diagnosis of tuberculosis endpoint 1
Recruitment and follow-up challenges

Challenges:

- Large sample size needed! Generally, a minimum of a few thousands in efficacy studies
- Long time to disease progression (2 years of follow-up is standard)
- Resources for follow-up: staffing, contact with participants, active case finding
- Is the disproportionate focus on adolescents and adults valid (BCG, transmission likelihood)?

Intention-to-treat vs. per-protocol analysis:

“Intention-to-treat (ITT) analysis maintained the original group composition achieved by randomisation”
“Per protocol (PP) analysis included only those participants who completed the protocol for their allocated treatment”
- Consolidated Standards of Reporting Trials (CONSORT) recommends ITT as standard practice in analysis of clinical trials

- Sedgwick, BMJ, 2015
Non-adherence in non-inferiority trials: pitfalls and recommendations. PMID: 32651165
TB Vaccinology Achievements in 2018 (1)
Prevention of Infection (BCG and H4): NCT02075203

Nemes, et al. NEJM, 2018
TB Vaccinology Achievements in 2018 (2)
Efficacy of GSK M72/AS01E (NCT01755598)

Promise for sub-unit TB vaccines

Van Der Meeren, et al. NEJM 2018
The Quest for the TB Correlates of Protection (COP)

Is the immune COP mechanistic (i.e. protection-driving), or just a passenger correlate?
Systems Biology: Biomarkers vs. Hypothesis Generation

Correlates:
Who is protected?

Mechanisms:
Why are they protected?
Special considerations to define COPs in people living with HIV (PLWH)

- **Endpoints may be different:**
  - POI: Latent infection detection tools are less optimal in PLWH
  - POD: paucibacillary disease, non-pulmonary presentations

- **Special safety considerations:**
  Risk from live attenuated vaccines should be carefully monitored

Unanticipated interactions with ARVs

---

Reference: Lancet HIV. PMID: 36240834 (2022)
“Mothers of children in Sirajganj, Bangladesh ($n = 60$), Shanghai, China ($n = 788$), Addis Ababa, Ethiopia ($n = 341$), Guatemala City and Quetzaltenango, Guatemala ($n = 767$), and Chandigarh, India ($n = 309$), completed a survey between 2016 and 2018 using the WHO’s 10-item Vaccine Hesitancy Scale.”

Decolonizing TB Vaccinology

Reference: PMID: 34097692

Courtesy of Madhu Pai