What would it take to eliminate tuberculosis by 2050?

Laith Abu-Raddad
Infectious Disease Epidemiology Group
Weill Cornell Medical College - Qatar
Cornell University
Doha, Qatar

Old technology for a lively disease

The technology for TB control:
- No new diagnostic test brought into wide use for over 100 years
- No new vaccine for 80 years
- No new drug brought into wide use for 40 years
The Bill & Melinda Gates Foundation

A $900 million pipeline of novel TB interventions: new diagnostics, new drugs, and a new vaccine

Some of these interventions in the Gates Foundation pipeline

- **Novel Vaccine:**
  - Infant vaccination boosted by adolescent vaccination

- **Novel Drugs:**
  - Moxifloxacin (4-month drug regimen but no efficacy against MDR or XDR TB)
  - Novel Regimen II (2-month regimen and efficacy against MDR and XDR TB)
  - Novel Regimen III (10-day regimen and efficacy against MDR and XDR TB)

- **Novel diagnostics:**
  - Mycobacteria Growth Indicator Tube (MGIT) culture
  - LED-fluorescence microscopy
  - Nucleic Acid Amplification Test (NAAT)
  - Dipstick for Antigen (Ag) or Antibody (Ab)
Mandate

What would it take in terms of a novel intervention, or combination of novel interventions, to eliminate TB by 2050?

Public Health Goal

TB elimination (< 1 TB disease case per million) in 2050
Impact of novel TB interventions

Collaboration

• Fred Hutchinson Cancer Research Center & University of Washington
• World Health Organization
• Gates Foundation

Methodology

• Working with developers to define the likely properties of their products
• Building a database of TB data
• Building a mathematical model incorporating all interventions
• Model analysis with a focus on the WHO Southeast Asia region
First phase:

*Modeling the impact of the developers’ products*

1. Impact of Novel Vaccine
Impact of a novel vaccine:
A vaccine with a full list of efficacies

A novel vaccine with:

- **Vaccine efficacy of 60%** against fast TB disease progression (VE$_P = 60\%$)

- **Other properties:**
  - Vaccine efficacy of 50% against TB disease progression among latently infected slow progressors (VE$_{PVLs} = 50\%$)
  - Vaccine efficacy of 50% against TB infectiousness (VE$_I = 50\%$)
  - Neonatal vaccination with an additional boost in adolescence
  - Mean duration of protection of 33 years
  - Vaccine coverage of 100%
  - Implementation in the year 2015

---

Impact of Novel Vaccine

![Impact of novel vaccine (complete list of efficacies)](image_url)
Impact of Novel Vaccine

Impact of novel vaccine (complete list of efficacies)

2. Impact of Novel Treatment
Impact of novel drug regimens: Novel drug regimen III

- Treatment duration of 10 days (instead of 6 to 9 months)
- Efficacy of 90% against drug-resistant TB disease
- Treatment success rate of 99% (compared to 84%)
Impact of Novel Treatment

3. Impact of Novel Diagnostics
Impact of novel diagnostics

A novel diagnostic with:

• Increased case detection rate
• Reduction of the time patients spend before diagnosis

LED-fluorescence microscopy

• Case detection rate (proportion) for sputum positive TB disease by about 10% (86% compared to 79% in the SEAR region)
• Time from onset of disease to diagnosis for sputum positive reduced by 29%
• No change for non-sputum positive TB disease
Impact of Novel Diagnostics

LED: DOTS-SP-CDR increased by 10%

SP incidence relative annual decline
SN incidence relative annual decline
NP incidence relative annual decline
TB mortality relative annual decline
Impact of the three novel interventions up to 2050

Why won’t the novel interventions do as well as hoped from them?
The TB infection congested highway

Thanks to Chris Dye

Long-term Impact of Vaccine

Impact of novel vaccine (complete list of efficacies)

SP disease incidence — SN disease incidence — NP disease incidence
Second phase:

Reconsideration of the interventions

What additional TB interventions will achieve the desired goal?

Vaccination:
- Mass vaccination instead of neonatal vaccination
- Post-exposure vaccination (therapeutic vaccine)

Treatment:
- Therapy of latent TB in addition to treatment of active disease
Impact of mass vaccination

Impact of novel vaccine (only the VE efficacy)

Impact of post-exposure vaccination

Post-exposure vaccination (efficacious among only slow progressors)
Mass latent therapy:

- Assuming essentially 100% efficacy of the drug to clear TB
- Universal coverage (essentially 100%)
Mass TB latent therapy

Impact of latency treatment (efficacious among only slow progressors)

A synergy of interventions
A measure of synergy

Synergy between mass vaccination and mass latent therapy

A conceptual map for synergy of interventions

Vaccination to reduce susceptibility to infection

Infection

Reinfection

Pre-exposure vaccination increasing fraction moving to latent slow

Latent therapy or post-exposure vaccination

Diagnostics and disease treatment

Recovery or Death

TB Disease

Susceptible

Latent Fast

Latent Slow
Conclusions

- **Novel diagnostics** are promising products in terms of TB control.
- Elimination is unlikely to be achieved without multiple interventions **simultaneously** affecting the **different** stages of TB natural history.
- Specifically, we need to address **TB disease as well as TB latent infection**.
- The return of investment is **highly optimized** when we administer synergistic multi-component interventions.

The End
The beginning of a story: Foundations phase

- Literature review of the natural history and epidemiology of TB infection
- Literature review of existing modeling work
- Essential collaboration with WHO (Chris Dye) for guidance and data
- Discussions with the developers in relation to the properties of their products
Impact versus efficacy of novel diagnostics in increasing case detection rate at 2050

Impact versus efficacy of novel diagnostics in increasing case detection rate at endemic equilibrium
Impact versus novel drug treatment success proportion at 2050

Long-term impact versus novel vaccine efficacy
Synergy measure

\[
\text{epidemiologic measure} = \begin{cases} 
> 1 & \text{synergy} \\
= 1 & \text{no synergy or redundancy} \\
< 1 & \text{redundancy}
\end{cases}
\]
Relative decline in incidence of mortality year by year up to 2050

Impact of novel regimen III

Impact of mass vaccination

Impact of novel vaccine (only the VEp efficacy)
Impact of Novel Diagnostics

Average duration of infectiousness of SP reduced by 50%

Impact of post-exposure vaccination

Post-exposure vaccination (efficacious among only slow progressors)
Impact of Novel Vaccine

Impact of novel vaccine (complete list of efficacies)

Impact of Novel Treatment

Impact of novel regimen III
A diagnostic that reduces the duration of infection

A product that reduces the time between onset of disease and diagnosis by 50%

Impact of Novel Diagnostics

Average duration of infectiousness of SP reduced by 50%

- SP disease incidence
- SN disease incidence
- NP disease incidence
- TB mortality incidence