Mathematical modelling to accelerate development of new tuberculosis vaccines

Preliminary Results

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Modelling to inform vaccine development

- Target product profiles (TPPs) and Preferred Product Characteristics (PPCs) guide strategic development of new TB vaccines to ensure new vaccines are fit for purpose and maximise future epidemiological impact.
- Insufficient evidence existed to guide decisions on key characteristics.
- When results become available from efficacy trials, value in estimating potential future epidemiological impact to guide decision making.
- Mathematical modelling as a logical framework
- Developed novel mathematical models to assess the population-level impact of new TB vaccines, delivered during 2025-2050 to adolescents and adults in China, South Africa and India.
Methods

- Age-structured compartmental dynamic model of *M. tb* transmission
- Calibrated to (where available) age- and HIV-stratified country-level TB prevalence, incidence, mortality and notifications data for China, South Africa and India.
- Accounted for private sector in India and HIV in SA
Calibrated models – Incidence Rate

China

South Africa

India

All

HIV positive

All-age incidence rate (/100,000 population)

Year

Incidence rate 0–14 years (/100,000 pop)

Year

Incidence rate 15+ years (/100,000 pop)

Year

Model

Data
Epidemiological outcomes

Proportion of new cases due to new infection vs reactivation/relapse of existing infection

China

South Africa

India

Proportion of All New Cases (%)

Year

Preliminary results
Vaccine Characteristics

VACCINE CHARACTERISTICS

POI* & POD

0-100% VE

2 yrs to lifelong

* Assumed POI vaccine is equally efficacious regardless of propensity for progression to disease upon infection
Vaccine Characteristics

Vaccine Characteristics:
- POI* & POD
- 0-100% VE
- 2 yrs to lifelong

Population:
- China
- South Africa
- India
- Routine 9yo
- Mass >9yo
- Pre-infection vs post-infection

Vaccine Deployment:
- 2025-2050
- 80% routine
- 70% mass

* Assumed POI vaccine is equally efficacious regardless of propensity for progression to disease upon infection
Outcome: Median incidence rate reduction (%) vaccine compared to no new vaccine baseline in 2050
Median incidence rate reduction (%) for pre- and post-infection vaccine compared to no new vaccine baseline in 2050, all with 10-yearly mass vaccination campaigns.
Median incidence rate reduction (%) for pre- and post-infection vaccine compared to no new vaccine baseline in 2050, all with 10-yearly mass vaccination campaigns (safe and equally effective in HIV positive populations in SA).

**South Africa**

Preliminary results

- POI vs POD efficacy varies by setting
- Relative importance of POI increasing in higher transmission settings
- 2 vs 5 years minimum duration of protection
Median incidence rate reduction (%) for pre- and post-infection vaccine compared to no new vaccine baseline in 2050, all with 10 years protection, 10-yearly mass vaccination campaigns.

Most variation comes from impact in pre-infection populations, with impact higher in transmission-driven epidemics.

**South Africa**

Preliminary results

**China**

**India**
Comparison of median incidence rate reduction (%) for pre- and post-infection vaccine with different HIV efficacy assumptions in SA

Preliminary results

Safe and equally effective in HIV

Safe but with 20% reduction in efficacy in HIV

NOT safe in HIV

In high-HIV settings, safety and efficacy in HIV-positive populations would help maximise impact
Impact estimates based upon BCG-revaccination results

<table>
<thead>
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Hatherill et al. Global vaccine Forum, 2018
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South Africa (no HIV efficacy)

South Africa (HIV efficacy)

Hatherill et al. Global vaccine Forum, 2018
Limitations

1. All models are an approximation of reality, and for vaccines the likely characteristics remain uncertain.
2. The results presented here are representative of the epidemics in the 3 settings.
3. Assumes POI would be efficacious regardless of likelihood of progression to disease if infected – unknown
4. SA work is still ongoing, so results are preliminary
Conclusions – Preliminary results

- In all 3 settings, for a P&PI vaccine **efficacy for prevention of disease** would have greatest impact over the 2025-2050 timeframe.

- In China (**reactivation** driven epidemic) prevention of **disease** efficacy was imperative for achieving substantial impact before 2050.

- In India and SA efficacy for **prevention of infection** could also substantially impact the TB epidemic over 2025-2050 (due to greater ongoing **transmission**).

- In SA, a 20% reduction in VE in **HIV positive** populations would reduce the overall impact of the vaccine, but not substantially.

- However, population-level impact in SA would be substantially reduced with a vaccine that is not safe or effective in HIV positive populations.
Conclusions – Preliminary results

• The minimum duration of protection to achieve 20-29% incidence reduction in 2050 was 5 years in China and South Africa, and 2 years in India.

• Increasing mass vaccination frequency could help maximise impact, but would require an assessment of feasibility and cost-effectiveness.

• Post-infection (effective in latency and recovered populations) vaccines provided a similar incidence rate reduction in all 3 settings.

• Importance of efficacy in pre-infection populations varied by setting:
  
  India > SA > China
Implications for vaccine development

For development strategists and clinical triallists:

• If population-level impact maximisation before 2050 is the aim, prevention of disease vaccines would be required in China.

• Importance of both efficacy for prevention of disease and for prevention of infection in the SA and India settings, therefore ideally both infection and disease endpoints would be measured in clinical trials. In India, evidence of prevention of infection could be sufficient (assuming vaccine efficacy is the same regardless of likelihood of progression to disease).

• In settings with high HIV prevalence, vaccines safe and effective in HIV-positive populations could add substantial population-level benefit.

• Duration of protection - with sufficient vaccine efficacy both South Africa and China would require at least 5 years protection, whereas 2 years may be sufficient in India – may want to reflect this in trial design.
**Implications for vaccine development**

*For country-level decision makers:*

- Planning for vaccination of older children/adolescents (co-administration with HPV?), and mass vaccination campaigns.
- If duration of protection was found to be low, planning for more frequent revaccination campaigns may help maximise population-level impact.
Population-level impact of future vaccines is dependent upon the underlying epidemiology.

The relative impact of vaccines effective against infection and disease, and in uninfected or latently infected populations needs to be considered in the context of the epidemiological setting to inform decision making for development strategy, trial design and implementation.

Depending on the vaccine - one size may not fit all
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