The potential public health impact of new TB vaccines

5th Global Forum on TB Vaccines

Richard White\textsuperscript{1,2}, Rebecca Harris\textsuperscript{2}, Chathika Weerasuriya\textsuperscript{2}

\textsuperscript{1} TB Modelling and Analysis Consortium

\textsuperscript{2} TB Modelling Group, London School of Hygiene and Tropical Medicine
I have the following, real or perceived, direct or indirect, conflicts of interest that relate to this presentation

<table>
<thead>
<tr>
<th>Affiliation / Financial interest</th>
<th>Nature of conflict / commercial company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco-industry and tobacco corporate affiliate related conflict of interest</td>
<td></td>
</tr>
<tr>
<td>Grants/research support (to myself, my institution or department):</td>
<td>Research grants to my Institution from: BMGF, Aeras, USAID, Global Fund, WHO, US CDC, UK MRC, UNITAID</td>
</tr>
<tr>
<td>Honoraria or consultation fees:</td>
<td></td>
</tr>
<tr>
<td>Participation in a company sponsored bureau:</td>
<td></td>
</tr>
<tr>
<td>Stock shareholder:</td>
<td></td>
</tr>
<tr>
<td>Spouse/partner – conflict of interest (as above):</td>
<td></td>
</tr>
<tr>
<td>Other support or other potential conflict of interest:</td>
<td></td>
</tr>
</tbody>
</table>
Modelling to inform vaccine development

- Mathematical modelling is a logical framework for informing vaccine development
  - by creating **best rationale prediction** for the influence of vaccine and implementation characteristics, on public health impact

- Summarise the available mathematical modelling evidence
  - Systematic review summarising 23 studies
  - + 4 studies published since review
  - + 2 unpublished studies exploring the impact of potential new TB vaccine characteristics in China, India and South Africa

Harris 2016, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017, Harris. in review & in prep
Summary of modelling evidence 1/3

Prevention of infection (POI) versus prevention of disease (POD)

- In low and middle income counties (LMICs) in general, and in China, before 2050, prevention of disease vaccines would provide faster and greater impact than prevention of infection.
- In contrast, in transmission-driven epidemics like India, before 2050, efficacy for prevention of infection or disease, could substantially impact the TB epidemic (assuming POI leads to POD).

Pre- versus post-infection

- Lit divided if pre- or post-infection vaccines would provide greatest impact.
  - Will depend upon prevalence of infection & balance of primary disease vs. reactivation disease.
- In ageing, reactivation-driven TB epidemics like China, before 2050, vaccines effective in individuals post-infection will be essential to maximise impact.
- Whereas, in transmission-driven epidemics like India, before 2050, pre-infection vaccines provided a similar impact to post-infection vaccines.

Summary of modelling evidence 2/3

• **Duration of protection**
  – In LMICs in general, before 2050, as little as 5 years protection may be cost effective, if delivered to adolescents/adults
  – In ageing, reactivation-driven TB epidemics like China, before 2050, with routine vaccination of 9yo and 10-yearly mass campaigns (≥9yrs), at least 5 years protection would be needed to achieve at least a 20-29% reduction in incidence rates
  – In transmission-driven epidemics like India, before 2050, shorter (2 years) protection could achieve similar level of impact

• **Vaccine efficacy**
  – In LMICs, before 2050, as low as 20% VE may be cost effective, if delivered to adolescents/adults

*Harris 2016, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017, Harris. in review & in prep*
Summary of modelling evidence 3/3

**Age at vaccination**

- **Neonatal**
  - In LMICs in general, before 2050, impact of neonatal vaccination was lower than adolescent/adult vaccination
  - To be cost effective, longer durations and higher vaccine efficacy (VE) would be required

- **Adolescent/adults**
  - In LMICs, before 2050, adolescent/adult vaccination provided greater and more rapid impact than neonatal vaccination, and was cost effective even at low vaccine efficacies and durations (e.g., VE 20%, 5 years protection)
  - In ageing, reactivation-driven TB epidemics like China, before 2050, adolescent vaccination had low impact as the majority of disease was in the elderly

- **Older adults**
  - In ageing, reactivation-driven TB epidemics like China, before 2050, an efficacious post-infection vaccine delivered to older adults will be critical to maximise population-level impact

Harris 2016, Shrestha 2016, Lui 2017, Arregui 2017, Shrestha 2017, Harris. in review & in prep
Summary over!

Illustration of key points
Prevention of infection vs prevention of disease

- In LMICs in general, and in China, before 2050, prevention of disease vaccines will provide faster and greater impact than prevention of infection.

- In contrast, in transmission-driven epidemics like India, before 2050, efficacy for prevention of infection or disease, could substantially impact the TB epidemic (assuming POI leads to POD).
Pre vs post infection efficacy

- Literature divided as to if pre-infection or post-infection vaccines would provide greatest impact
  - Will depend upon prevalence of infection & balance of primary disease vs. reactivation disease
- In ageing, reactivation-driven TB epidemics like China, before 2050, vaccines effective in individuals post-infection (PSI) will be essential to maximise impact
- In contrast, in transmission-driven epidemics like India, before 2050, pre-infection (PRI) vaccines provided a similar impact to post-infection (PSI) vaccines

Harris et al. 2016, Harris et al., In prep
Age at vaccination - LMICs

**Neonatal**
- In LMICs before 2050, impact of neonatal vaccination was lower than adolescent vaccination.
- Required lifelong, high VE to be cost effective
- **Infant vaccination** would have **delayed epidemiological impact** due to lower burden and infectiousness in children

**Adolescent/adult**
- In LMICs, before 2050, adolescent/adult vaccination provided **greater and faster** impact
- Cost effective even at low vaccine efficacies and durations (VE 20%, 5 years protection)

Prevent 0.89 million (range 0.42-1.58m) 2024-50

Knight et al. PNAS, 2014
In LMICs, to reduce TB in 0-4 years olds, targeting adolescents/adults, may have quicker impact than targeting <1 year olds

- Extending Knight et al, PNAS, 2014 (pre and post efficacy, POD vaccine)
- To reduce TB in 0-4 year olds, vaccinating adolescents/adults, may be as effective, or more effective, than vaccinating neonates
- Because indirect effect of reducing the force of infection on infants, by vaccinating adolescents/adults, greater than direct effect of vaccinating infants
**Age at vaccination - China**

**Adolescents (15-19yrs)**
- In China, before 2050, as the majority of disease already in the elderly, adolescent vaccination alone provided low impact

**Older adults (60-64yrs)**
- An efficacious, post-infection, vaccine delivered to older adults, will be critical to maximise population-level impact

*Harris et al., in review*
Limitations

- Simplification of very complex reality
- Projecting long periods into the future, during which scale up/development of other control measures will alter epidemic
- We explore a wide range of vaccine characteristic assumptions, but characteristics of vaccines we can actually develop, are unknown
Implications for new TB vaccines

LMICs

For clinical triallists and development strategists (e.g. WHO, cross-product bodies, developers)

- **POI/POD** - Protection against disease will be key to achieving most rapid impact up to 2050, therefore POD trial endpoints important

- **Pre- versus post-infection** – Relative impact depends on local epidemiology. If feasible, trials should be powered to assess efficacy in pre and post infection populations

- **Vaccine efficacy** – Assess feasibility of designing trials to detect lower vaccine efficacies (e.g. 20%)

- **Duration of protection** – Long term follow up still required for implementation design, but shorter durations (e.g. 5 years) may be cost-effective

- **Age of vaccination** – If maximum population-level impact by 2050 is the goal, development of vaccines for adolescents/adults important (including older adults in China-like populations)

For country-level decision makers

- Consider **vaccination platforms for adolescents** (HPV?), and **feasible frequency of mass campaigns for adults**
Implications for new TB vaccines

India

As LMIC, except

For clinical triallists and development strategists (e.g. BMGF, WHO, cross-product bodies, developers)

• POI/POD
  – Both efficacy for prevention of disease and for prevention of infection important (assuming POI leads to POD) => ideally measure both in trials
  – Vaccine demonstrated to have POI or POD efficacy could have important epidemiological impact (assuming POI leads to POD)

• Duration of protection – High potential population level impact in India, suggests shorter duration of follow-up may be acceptable
Other modelling results at conference

Other modelling work at conference

1. **Updating the recommended age of BCG vaccination? Modelling the potential impact on global paediatric TB mortality.** Tue 20th 1615-1745 Room: Sheesh Mahal; Dr Patho Roy

2. **Animal dose response curve predicts lower optimal tuberculosis vaccine dose in humans: The use of vaccine Immunostimulation/Immunodynamic modelling methods to inform vaccine dose decision-making.** Wed 21st 1630-1800 Room: Roshanara; Dr Sophie Rhodes

3. **Maximising impact of the TB vaccine pipeline – mathematical modelling to inform target product profiles.** Thur 22nd 1130-1300 Room: Jehangir; Dr Rebecca Harris

Future modelling

Future

1. **MDR TB – Impact and cost effectiveness of new prophylactic TB vaccines** [Funded, Aeras, by end 2018]

2. **MDR TB – Impact and cost effectiveness of new therapeutic TB vaccines** [Proposed]

3. **Dose finding – within-host PK/PD modelling to inform vaccine dose size** [Ongoing]

4. **Assessing the impact of vaccines in the context of other new interventions** [Funded, MRC, by 2020]
Acknowledgements and Thanks!

Contributors/Advisors:

- WHO (Johan Vekemans, Gitte Giersing)
- Aeras (Jacqui Shea, Vicky Cardenas, Tom Evans, Ann Ginsburg, Danny Casimiro, Chen Chen, Sharon Chan)
- BMGF (Willem Hanekom, Anne Kasmar)
- TBVI (Bernard Fritzell, Nick Drager)
- China (Dr. Li tao and Prof Lixia Wang)
- South Africa (Gavin Churchyard TBC)

Funders: