Enriching Cohorts for Smaller, Quicker, More Efficient TB Vaccine Studies

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Introduction

- Optimal efficacy endpoint for TB vaccine studies is prevention of TB disease (POD)
  - POD efficacy studies require 1000s of participants and lengthy follow up to accrue disease endpoints
- No correlates of risk currently that can be used for selecting trial participants
- TB vaccines enter advanced clinical trials with safety and immunogenicity data but limited data supporting efficacy
Information on candidates in clinical development is self-reported by vaccine sponsors, coordinated by the Working Group on New TB Vaccines and updated September 2017.
Target Populations

- Infants (healthy)
- Adolescents/Adults (healthy)
- TB patients
• Identify populations at higher risk of TB infection and/or disease than the general population
• These enriched populations will allow for smaller, quicker and more efficient studies
• Triaging tool for up/down candidate selection prior to conduct of large Phase 3 registration studies
  – Resource sparing
Identification of High Risk Groups – with focus on POD

• Populations identified by literature reviews and personal communications with key experts
• Using published data from these populations, evaluated their suitability for efficacy trials
• Prime considerations included:
  – Ease of recruitment
  – Potential for reduced sample sizes and/or quicker studies
  – Feasibility of study design/conduct
### Potential High Risk Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Estimated Increased Relative Risk TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miners</td>
<td>~4-fold</td>
</tr>
<tr>
<td>HIV Infected Individuals</td>
<td>7 - 26-fold (much lower in ART era)</td>
</tr>
<tr>
<td>Diabetics</td>
<td>3-fold</td>
</tr>
</tbody>
</table>
# Potential High Risk Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Estimated Increased Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prisoners</td>
<td>3 - 151 for TB disease&lt;br&gt;5 – 84 for TB infection</td>
</tr>
<tr>
<td>LTBI+ with SOR for progression to disease</td>
<td>~7-fold in 18 months prior to TB disease</td>
</tr>
<tr>
<td>Prevention of Recurrence</td>
<td>2-8% per annum in the two years following treatment</td>
</tr>
</tbody>
</table>
### Potential High Risk Populations

<table>
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<tr>
<th>Population</th>
<th>Estimated Increased Relative Risk</th>
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<tbody>
<tr>
<td>House-hold contacts (HHCs)</td>
<td>2 - 50 for TB disease 2 - 83 for TB infection</td>
</tr>
<tr>
<td>Health-care workers (HCWs)</td>
<td>2 - 18 for TB disease 8 - 21 for TB infection</td>
</tr>
</tbody>
</table>
TB Disease in Health Care Workers (HCWs)

- Risk of increased transmission and disease in HCWs has been recognized for many years worldwide.
- In low- and middle income countries annual incidence of TB disease in HCWs 0.5% to 14%\(^1\)
- TB disease incidence higher than in the general population
  - incidence rate ratio (IRR) 1.4 to 20.0 (2 of 20 studies IRR of 0.7)\(^2\)
  - Median estimated IRRs for high TB incidence countries 5.4\(^3\)
- Clearly defined categories of HCWs have higher risk\(^2\)
- Strong association between implementation of TB infection control programmes and reduced nosocomial transmission\(^1\)

\(^1\)McCarthy et al, 2015; \(^2\)Joshi et al, 2006; \(^3\)Baussano et al, 2011
# Prevention of TB Disease in Health Care Workers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Naidoo et al\textsuperscript{ref}</th>
<th>Phase 2b POD Trial in QFT+ Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB disease incidence</td>
<td>1.1%/annum</td>
<td>0.55%/annum</td>
</tr>
<tr>
<td>Sample Size*</td>
<td>1754</td>
<td>3506</td>
</tr>
<tr>
<td>Duration</td>
<td>4 years</td>
<td>4 years</td>
</tr>
</tbody>
</table>

\*Sample size - vaccine efficacy (70\%), power (80\%), type 1 error (10\% 2-sided) will require 21 endpoints. Assume LTFU (15\% over 2 years), length of follow-up (3 years).
Prevention of TB Disease in Household Contacts

- Previously been used to evaluate efficacy of BCG\(^1\)
- Variable definition
  - individuals living in same household as adult/adolescent index case at least 3 months (for 7 days) prior to TB diagnosis; sharing meals; identifying common household head
- Establishing cohorts may be time-consuming and expensive compared to cohorts from general population

\(^1\)Rosenthal et al, 1961
Prevention of TB Disease in HHCs - Considerations for Study Design

- Co-prevalent disease rates (definitions variable) are high
  - 1.4\(^1\); 9.2\(^2\); 4.2\(^3\) of recruited cohort have co-prevalent disease
  - 56\(^1\) and 67\(^3\) of TB cases co-prevalent

- Depending on setting, prevalence and incidence of HIV may be a significant issue
  - 17.9\(^1\) prevalence and incidence 2.2/100py
  - TB disease incidence by HIV status at baseline – HIV+ 5.4/100py; HIV- 0.7/100py\(^1\)
  - 52\(^2\) of incident cases HIV positive

\(^1\)Hill et al, 2008; \(^2\)Van Schalkwyk et al, 2014; \(^3\)Guwatudde et al, 2003
Conclusions

• Trials already being conducted in higher risk populations
  – An ongoing Phase 2b POD trial (TB-018; M72) utilizes a population at higher risk of disease than general population (IGRA+)
  – Prevention of recurrence trial (VPM1002) initiated in India

• Other populations at very high risk of infection and/or disease have been identified and should be considered for TB vaccine clinical trials
Thank You