BCG revaccination: trial endpoints & potential policy impact

Gavin Churchyard
MBBCh (WITS), FCP (SA),
FRCP (Edin), MMED (WITS), PhD (WITS)
The Aurum Institute
Honorary Professor, School of Public Health, University of Witwatersrand
Adjunct Professor, Department of Medicine, Vanderbilt University
Overview

• Background
  o TB epidemiology
  o Neonatal BCG
    – Prevention of disease
    – Prevention of infection

• BCG revaccination
  o POD
  o POI
  o Endpoints
  o Policy impact

• Conclusion

(Harris, Science Translational Medicine, 2020)
Background

- Epidemiology
- Non-tuberculous mycobacteria
- TB vaccine strategies
Background
TB epidemiology

- ~24% of world's population is TB infected
  - >3% recently infected
  - Prevalence of TB infection among adolescents in high burden countries varies
    - Low in China: 3%
    - Intermediate in Uganda: 16%
    - High in South Africa: 49%

- Risk of TB disease greatest in the first two years after infection

- Pulmonary TB is responsible for TB transmission
Background

Non-tuberculous mycobacteria

Distributions of TST responses in children

(Dye, J R Soc Interface. 2013)
Background

TB vaccination strategies

(Hatherill. Frontiers in Microbiology. 2020)
BCG vaccination of infants & children

- Prevention of disease
- Prevention of infection
BCG vaccination of infants & children

Prevention of disease

- BCG is efficacious in preventing TB meningitis & military TB
- BCG provides variable protection against pulmonary TB (0%-80%)

(Mangtani, CID, 2014)
BCG vaccination of infants & children

Prevention of disease

- BCG does not protect against TB disease when given to people with TB infection
- Provides protection for ~10 years, but may exceed 15 years
- Is recommended by WHO soon after birth in high burden countries
- Universal BCG coverage has had little impact TB disease burden

(Global TB report, 2016)

(BCG atlas, 2017)
BCG vaccination of infants & children

*Prevention of infection*

- Previously it was not possible to determine whether BCG vaccination
  - Protected against disease by preventing infection
  - Prevented progression from infection to disease

- IGRAs can identify
  - TB infection distinct from BCG vaccination & NTM infection
  - Initial & sustained conversion
  - Reversions
  - Quantitative levels
BCG vaccination of infants & children

Prevention of infection

• A systematic review & meta-analysis was conducted to determine whether pre-exposure BCG vaccination of infants & children protects against TB infection
• Studies included vaccinated and unvaccinated children <16 years with known recent exposure to a person with pulmonary TB
• Primary analysis included 14 studies

(Roy, BMJ, 2014)
### BCG vaccination of infants & children

**Prevention of infection**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No of studies</th>
<th>Risk ratio (95% CI)</th>
<th>I² (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>14</td>
<td></td>
<td>40</td>
<td>0.81 (0.71 to 0.92)</td>
</tr>
<tr>
<td><strong>Type of test (P=0.85)</strong></td>
<td></td>
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<tr>
<td>ELISPOT</td>
<td>4</td>
<td></td>
<td>52</td>
<td>0.83 (0.68 to 1.02)</td>
</tr>
<tr>
<td>Quantiferon</td>
<td>10</td>
<td></td>
<td>43</td>
<td>0.78 (0.64 to 0.96)</td>
</tr>
<tr>
<td><strong>Latitude (P=0.56)</strong></td>
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<td></td>
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</tr>
<tr>
<td>&lt;20</td>
<td>4</td>
<td></td>
<td>49</td>
<td>0.87 (0.72 to 1.04)</td>
</tr>
<tr>
<td>20-40</td>
<td>2</td>
<td></td>
<td>54</td>
<td>0.88 (0.54 to 1.45)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>8</td>
<td></td>
<td>34</td>
<td>0.74 (0.60 to 0.91)</td>
</tr>
</tbody>
</table>

(Roy, BMJ, 2014)
BCG revaccination of adolescents

- Age specific TB epidemiology
- Justification
- Prevention of disease
- Prevention of infection
• Among adolescents and adults in high transmission settings
  o The risk of TB infection increases substantially due to social mixing
  o TB incidence is high, particularly those with IGRA/TST conversion
• BCG protection wanes by pre-adolescence

(Wood, PLoS ONE, 2011)
Among adolescents and adults in high transmission settings
  - The risk of TB infection increases substantially due to social mixing
  - TB incidence is high, particularly those with IGRA/TST conversion

- **BCG protection wanes by pre-adolescence**

BCG revaccination of adolescents

Justification

- Pre-exposure revaccination of TST-/IGRA- adolescents & adults may
  - Boost immune responses that protect against TB infection
  - Provide durable protection against developing TB disease
  - Interrupt TB transmission
  - Achieve population level impact on TB control & be cost effective
Systematic reviews

- WHO position paper, 2004, BCG revaccination not recommended
- Barreto, J Pediatr, 2006. No evidence to support revaccination
- Ahmad, 2013: 9 studies (4 RCTS) no benefit from revaccination
- SAGE, 2017 (3 studies (2 RCT)) Revaccination not recommended

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Vaccine Strain</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodrigues et al., 2005</td>
<td>RCT</td>
<td>BCG- Moreau</td>
<td>Children in Brazil</td>
</tr>
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<tr>
<td>Karonga Prevention Trial Group, 1996</td>
<td>RCT</td>
<td>BCG-Glaxo</td>
<td>Individuals in Malawi</td>
</tr>
<tr>
<td>Leung et al., 2012</td>
<td>Observational</td>
<td>BCG-Glaxo</td>
<td>Primary school children in Hong Kong</td>
</tr>
<tr>
<td>Tala-Heikkila et al., 1998</td>
<td>Observational</td>
<td>BCG-Glaxo</td>
<td>Children 11 to 13 years old in Finland</td>
</tr>
<tr>
<td>Sepulveda et al., 1992</td>
<td>Observational</td>
<td>BCG- Pasteur</td>
<td>Young adults in Chile</td>
</tr>
</tbody>
</table>
Proof of concept trials

• **Strengths**
  o It is plausible that controlling initial TB infection will reduce the risk of TB disease
  o POI trials will be smaller, shorter & cheaper than POD
  o Can be used to select candidates for phase III trials

• **Limitations**
  o POI may not translate into POD
  o POI may be among the 90% of people unlikely to develop TB disease
  o A vaccine that protects against disease may not protect against infection
Proof of concept trials

Endpoints

Among South African adolescents, the risk of developing TB among QFT converters (IFN-γ (TB Ag-Nil) >0.35IU/ml) is ~9x higher than non-converters.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>n</th>
<th>TB Incident Cases</th>
<th>Observation Time (person-yr)</th>
<th>Incidence Rate per 100 person-yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TB cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QFT converters</td>
<td>534</td>
<td>15</td>
<td>1,026</td>
<td>1.46 (0.82–2.39)</td>
</tr>
<tr>
<td>QFT nonconverters</td>
<td>629</td>
<td>2</td>
<td>1,169</td>
<td>0.17 (0.02–0.62)</td>
</tr>
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<td>Protocol-defined TB cases</td>
<td></td>
<td></td>
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<td>629</td>
<td>1</td>
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</tr>
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(Machingaidze, Am J Respir Crit Care Med, 2012)
BCG revaccination of adolescents
Prevention of infection

Proof of concept trials

- **Endpoints**
  - The risk of TB increases with more stringent definitions of conversion
    - IFN-γ (TB Ag-Nil) > 4 IU/ml

<table>
<thead>
<tr>
<th>QFT Class</th>
<th>Incidence (Cases/100 Person-Years)</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
<th>IRR</th>
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<tr>
<td>Stringent nonconverters*</td>
<td>0.16</td>
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<td>Reference</td>
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</tr>
<tr>
<td>Stringent persistent positives</td>
<td>0.97</td>
<td>(0.59–1.52)</td>
<td>0.005</td>
<td>6.27</td>
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<td>Stringent converters†</td>
<td>1.60</td>
<td>(0.88–2.69)</td>
<td>0.0003</td>
<td>10.33</td>
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<tr>
<td>“Uncertain” converters§</td>
<td>0.66</td>
<td>(0.14–1.95)</td>
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<td>4.27</td>
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*IFN-γ (TB Ag – Nil) greater than 0.7 IU/ml at Days 0, 360, and 720.
†IFN-γ (TB Ag – Nil) less than 0.2 IU/ml at Day 0 and IFN-γ greater than 0.7 IU/ml at Day 360.

**Proof of concept trials**

**Endpoints**

- The risk of TB increases with more stringent definitions of conversion
  - IFN-γ (TB Ag-Nil) >4IU/ml

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Proof of concept trials

- **Endpoints**
  - The risk of TB increases with more stringent definitions of conversion
    - IFN-γ (TB Ag-Nil) >4IU/ml
BCG revaccination of adolescents
Prevention of infection

Phase 2 RCT

• 990 adolescents living in Cape Town, SA, BCG vaccinated at birth
• Randomized to H4:IC31 vaccine or BCG revaccination, placebo
• All participants were QFT negative & HIV negative at enrollment
• QFTs performed 6 monthly for 2 years
• Primary outcomes: safety and initial conversion
• Secondary outcomes: immunogenicity & sustained QFT conversion

First BCG revaccination trial to enroll participants based on TB infection status with repeated QFTs

(Nemes, NEJM, 2018)
BCG revaccination of adolescents
Prevention of infection

Phase 2 RCT

- BCG did not prevent initial conversion
- BCG prevented sustained infection

(Nemes, NEJM, 2018)
BCG revaccination of adolescents

*Prevention of infection*

Exploratory efficacy endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>QFT Conversion Threshold</th>
<th>BCG Group</th>
<th>Placebo Group</th>
<th>Vaccine Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15.2 to 59.8</td>
<td>-3.3 to 67.0</td>
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<tr>
<td></td>
<td></td>
<td>(0.03)</td>
<td>(0.06)</td>
<td></td>
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<tr>
<td>Exploratory outcome</td>
<td></td>
<td>31/310</td>
<td>(10.0)</td>
<td></td>
</tr>
<tr>
<td>Sustained QFT conversion**</td>
<td>&lt;0.2 to &gt;0.7</td>
<td>19/312</td>
<td>41.6↓</td>
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<td></td>
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<td>(6.1)</td>
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<td>31/310</td>
<td>(10.0)</td>
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<tr>
<td>End-of-trial sustained QFT conversion††</td>
<td>≥0.35</td>
<td>20/312</td>
<td>48.2↓</td>
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<td></td>
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<td>(6.4)</td>
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<td></td>
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<td>25.9 to 63.8</td>
<td>10.5 to 70.0</td>
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<td></td>
<td></td>
<td>(0.008)</td>
<td>(0.02)</td>
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<tr>
<td></td>
<td></td>
<td>36/310</td>
<td>(11.6)</td>
<td></td>
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<tr>
<td>QFT conversion‡‡</td>
<td>&gt;4.0</td>
<td>19/312</td>
<td>45.1‡</td>
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<td>20.5 to 62.2</td>
<td>3.8 to 69.3</td>
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<td></td>
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<td>(0.04)</td>
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<tr>
<td></td>
<td></td>
<td>33/310</td>
<td>(10.6)</td>
<td></td>
</tr>
</tbody>
</table>

(Nemes, NEJM, 2018)
Phase 2 RCT

- **Safety & immunogenicity**
  - Adverse events were more common in the BCG arm
    - 98% of participants had one or more adverse event
  - BCG associated with mild to moderate injection site reactions
  - No difference in severe & serious AEs by study arm
  - BCG revaccination was immunogenic & boosted BCG-specific CD4+ T-cell responses

(Nemes, NEJM, 2018)
**BCG revaccination of adolescents**

*Prevention of infection*

**BCG REVAX phase 2b RCT (NCT04152161)**

- **Aim:** to evaluate the efficacy, safety, and immunogenicity of BCG revaccination in adolescents for the prevention of sustained TB infection over 4 years
- **Primary efficacy endpoint:** Sustained QuantiFERON®-TB Gold Plus conversion using a cut-off Value of 0.35 IU/mL
- **Eligibility criteria:** ≥ 10 years and ≤ 18 years
- **Sample size:** 2150
- **5 sites (3 in Western Cape, 1 Durban, 1 in Johannesburg)**
Prevention of infection & disease

Pre-exposure vaccination of infants & children

BCG protects against TB infection as well as progression from infection to disease

(Roy, BMJ, 2014)
Modelled impact & policy implications

- Pre-exposure vaccines
- HIV impact
Modelled vaccine efficacy
TB uninfected populations

(Vaccine efficacy against disease)
(Vaccine efficacy against infection)

China
South Africa
India

(Harris, Sci. Transl. Med, 2020)
Conclusion

BCG revaccination

- Is safe & immunogenic
- Prevents sustained TB infection
- If BCG revaccination is effective in preventing TB infection and disease, it may deliver substantial population level impact in high transmission settings, particularly if combined with an effective post-exposure TB vaccine
Acknowledgements

- Mark Hatherill
- Richard White