Vaccination following mycobacterial exposure

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What do we understand by “mycobacterial pre-sensitization”

TST

IGRA
Many new TB vaccine candidates are targeted at adolescents/adults

Knight et al., PNAS 2014

LIC Infant

Duration of protection

Efficacy

Cost in US$

LIC Adolescent/Adult

Duration of protection

Efficacy

Cost in US$

Cost-effectiveness “threshold”

Knight et al., PNAS 2014
Many new TB vaccine candidates are targeted at adolescents/adults

1. Adolescents are (highly) sensitized to mycobacteria

2. In S. Africa, at least 50% are infected (TST+, IGRA+)

Nemes et al., AJRCCM 2017
040-404 adolescent screening cohort
Sensitization of children

North India

South Africa

Dye, J. R. Sco. Int 2013
Take home #1

Immunological sensitization to mycobacteria is very common (but depends on the setting)
Mycobacterial pre-sensitization is associated with reduced vaccine efficacy of BCG

BCG vaccination of sensitized population masks vaccine efficacy

Mangtani et al., CID. 2014
What do we understand by “mycobacterial pre-sensitization”

<table>
<thead>
<tr>
<th>Disease progression</th>
<th>Quiescent infection</th>
<th>Incipient disease</th>
<th>Subclinical disease</th>
<th>Active disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological sensitization</td>
<td>Low-level bacterial replication</td>
<td>Moderate bacterial replication</td>
<td>Moderate to high bacterial replication</td>
<td></td>
</tr>
<tr>
<td>Bacterial replication controlled</td>
<td>Asymptomatic without radiological or microbiological evidence of disease</td>
<td>Asymptomatic with radiological or microbiological evidence of disease</td>
<td>Clinical signs &amp; symptoms</td>
<td></td>
</tr>
<tr>
<td>successfully</td>
<td></td>
<td></td>
<td>Radiological and/or microbiological evidence of disease</td>
<td></td>
</tr>
</tbody>
</table>

- >12 months
- 3-6 months
- 0 months

**Inflammatory processes**
- IFN response
- Complement cascade
- Myeloid inflammation
- Coagulation cascade
- Myeloid and lymphoid cells
- Neutrophils
- Tissue remodeling

Scriba, Penn-Nicholson, et al., PLOS Pathogens. 2017
How does prior immunological sensitization inhibit vaccine efficacy?

**The good:** the anti-mycobacterial response already provides protection, which vaccination does not improve upon (masking)

**The bad:** The anti-mycobacterial response clears/neutralises the vaccine such that a protective response cannot be induced (blocking)
The good: M.tb pre-sensitization protects against TB upon re-exposure

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Incidence Rate Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geer 1934</td>
<td>0.21 [0.02 – 2.03]</td>
</tr>
<tr>
<td>Geer 1934</td>
<td>0.04 [0.03 – 0.04]</td>
</tr>
<tr>
<td>Heimbeck 1938</td>
<td>0.58 [0.33 – 1.02]</td>
</tr>
<tr>
<td>Heimbeck 1938</td>
<td>0.22 [0.10 – 0.50]</td>
</tr>
<tr>
<td>Heimbeck 1938</td>
<td>0.12 [0.08 – 0.17]</td>
</tr>
<tr>
<td>Myers 1940</td>
<td>0.59 [0.26 – 1.33]</td>
</tr>
<tr>
<td>Myers 1941</td>
<td>0.25 [0.05 – 1.32]</td>
</tr>
<tr>
<td>Hastings 1941</td>
<td>0.15 [0.02 – 1.41]</td>
</tr>
<tr>
<td>Brehdy 1941</td>
<td>0.08 [0.03 – 0.23]</td>
</tr>
<tr>
<td>Israel 1941</td>
<td>0.51 [0.27 – 0.94]</td>
</tr>
<tr>
<td>Wright 1941</td>
<td>0.04 [0.03 – 0.04]</td>
</tr>
<tr>
<td>Schwartz 1942</td>
<td>0.16 [0.02 – 1.09]</td>
</tr>
<tr>
<td>Daniels 1944</td>
<td>0.18 [0.12 – 0.29]</td>
</tr>
<tr>
<td>Lim–Yuen 1946</td>
<td>0.21 [0.05 – 0.85]</td>
</tr>
<tr>
<td>Madsen 1942</td>
<td>0.13 [0.06 – 0.22]</td>
</tr>
<tr>
<td>Madsen 1942</td>
<td>0.19 [0.08 – 0.45]</td>
</tr>
<tr>
<td>Holm 1948</td>
<td>0.47 [0.13 – 1.66]</td>
</tr>
<tr>
<td>Thompson 1949</td>
<td>0.42 [0.18 – 0.98]</td>
</tr>
<tr>
<td>Badger 1949</td>
<td>0.57 [0.34 – 0.95]</td>
</tr>
<tr>
<td>Dickie 1950</td>
<td>0.23 [0.08 – 0.70]</td>
</tr>
<tr>
<td>Dickie 1950</td>
<td>0.23 [0.03 – 1.87]</td>
</tr>
<tr>
<td>Poole 1964</td>
<td>0.32 [0.15 – 0.69]</td>
</tr>
<tr>
<td>Karns 1959</td>
<td>0.41 [0.11 – 1.50]</td>
</tr>
</tbody>
</table>

Random Effects Model

0.21 [0.14 – 0.30]
Take home #2

Natural immunity induced by *M.tb* infection can protect against reinfection

Can we improve on this immunity?

How does this sensitization affect vaccination in terms of

  Tolerability?

  Immunogenicity?

  Efficacy?
Vaccine tolerability

BCG re-vaccination is well tolerated in *Mtb*-infected individuals

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>INH before BCG (n=33) #</th>
<th>Observation before BCG (n=39) #</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>10</td>
<td>17</td>
<td>0.70</td>
<td>0.34–1.37</td>
</tr>
<tr>
<td>Redness</td>
<td>26</td>
<td>28</td>
<td>1.19</td>
<td>0.81–1.42</td>
</tr>
<tr>
<td>Swelling</td>
<td>2</td>
<td>4</td>
<td>0.59</td>
<td>0.08–3.57</td>
</tr>
<tr>
<td>Induration</td>
<td>28</td>
<td>36</td>
<td>0.92</td>
<td>0.80–1.10</td>
</tr>
<tr>
<td>Ulcer</td>
<td>30</td>
<td>33</td>
<td>1.07</td>
<td>0.88–1.23</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>3</td>
<td>7</td>
<td>0.51</td>
<td>0.11–2.00</td>
</tr>
<tr>
<td>Pain + redness</td>
<td>8</td>
<td>17</td>
<td>0.56</td>
<td>0.24–1.17</td>
</tr>
<tr>
<td>Induration + ulcer</td>
<td>25</td>
<td>33</td>
<td>0.90</td>
<td>0.71–1.15</td>
</tr>
<tr>
<td>Redness + induration + ulcer</td>
<td>20</td>
<td>26</td>
<td>0.91</td>
<td>0.61–1.33</td>
</tr>
</tbody>
</table>

*n* = all subjects that received BCG vaccination.

RR = relative risk.

Hatherill et al., Vaccine 2014
Vaccine tolerability

AE profile not different by infection status

- H1:IC31 (Mearns et al., 2017)
- H56:IC31 (Luabeya et al. 2015 and Suliman submitted)

AE profile different by infection status

- M72:AS01E, more GI, headaches, myalgia and fevers (Penn-Nicholson et al., 2015)
Vaccine immunogenicity

Viral vector (MVA85A)

Scriba, Tameris et al., AJRCCM 2012
Vaccine immunogenicity

Protein-subunit (H1:IC31)

Ag85B

ESAT-6

Mearns and Geldenhuys et al., Vaccine 2016
Vaccine immunogenicity

Protein-subunit (M72:AS01$_E$)

Graphs showing immune responses over time.

Penn-Nicholson, Geldenhuys et al., Vaccine 2016
Vaccine immunogenicity

Protein-subunit (M72:AS01$_E$)

Day 7

QFT-

p=0.002

QFT+

Day 30

p=0.0255

Day 37

Day 60

p=0.0203

Day 210

Pie slices as number of cytokines expressed

4 3 2 1

Pie arcs: IFN-γ IL-2 TNF-α IL-17

Penn-Nicholson, Geldenhuys et al., Vaccine 2016
Take home #3

Prior mycobacterial sensitization can have effects on

- Vaccine safety
- Vaccine immunogenicity, longevity and the response profile
- Some level of sensitization can be overcome (even with BCG)
- We need to do better than M.tb infection
Conclusions

• Mycobacterial sensitization starts with BCG vaccination in most countries (i.e. it is here to stay for some time)

• BCG re-vaccination of persons with mycobacteria-specific immune responses can prevent sustained infection

• Preventing disease progression in \textit{M}.\textit{tb}-infected persons will need vaccines that can do better than natural immunity to \textit{M}.\textit{tb}

• If the target population for vaccination is largely already \textit{M}.\textit{tb}-infected, we have to develop better pre-clinical models for this