BCG:
What have we learnt in 100 years?

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What we thought we knew?

• Safe
• Reliable protection against disseminated disease
• No effect of boosting on protection against disease
• Protection against leprosy
• Association with reduction in all cause mortality
• Intravesical installation for bladder cancer
Pooled rate ratios for pulmonary tuberculosis, according to trial characteristics.

**Trial attribute**

<table>
<thead>
<tr>
<th>Latitude</th>
<th>RR (95% CI)</th>
<th>$\tau^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>40°+</td>
<td>0.32 (0.22, 0.46)</td>
<td>0.117</td>
</tr>
<tr>
<td>20°&lt;40°</td>
<td>0.68 (0.48, 0.95)</td>
<td>0.019</td>
</tr>
<tr>
<td>0°&lt;20°</td>
<td>0.78 (0.58, 1.05)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

**Age at vaccination / tuberculin testing**

| Neonatal vaccination | 0.41 (0.29, 0.58) | 0.007 |
| School age vaccination - stringent tuberculin testing | 0.26 (0.18, 0.37) | 0.048 |
| School age vaccination - non stringent tuberculin testing | 0.59 (0.35, 1.01) | 0.095 |
| Other age vaccination - stringent tuberculin testing | 0.88 (0.59, 1.31) | 0.000 |
| Other age vaccination - non stringent tuberculin testing | 0.81 (0.55, 1.22) | 0.091 |

**Diagnostic detection bias**

| Lower risk of bias | 0.40 (0.25, 0.64) | 0.517 |
| Higher risk of bias | 0.78 (0.63, 0.95) | 0.000 |

**BCG strain**

| DU1-DU2-IV | 0.53 (0.15, 1.92) | 0.834 |
| DU2-III | 0.59 (0.31, 1.14) | 0.505 |
| DU2-IV | 0.41 (0.26, 0.66) | 0.316 |
| Not stated | 0.76 (0.24, 2.37) | 0.505 |

Mangtani et al, CID 2013
The magnitude of the BCG-attributable increase in IFNγ correlates with known protective efficacy.

Malawi

UK

Black et al, The Lancet 2002
Protection against *M. tb* infection as determined by QuantiFERON in children vaccinated with BCG.

~15% protection

Roy et al, BMJ 2014
What do we now know?

- Less safe in some populations (Hessling)
- Protection can be durable (Abubakar)
BCG IFN-γ ELISPOT and Ag85A IgG are immune correlates in BCG-vaccinated infants

BCG-IFN-γ ELISPOT

OR 0.502, p = 0.013

Fletcher HA et al Nature Communications, 2016

estimated odds ratio 0.62, p = 0.019
BCG revaccination reduces rate of sustained QFT conversion in South African adolescents

Nemes et al, NEJM 2018
BCG revaccination in school children in Brazil does not enhance protection against TB disease

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Pulmonary tuberculosis</th>
<th>Non-pulmonary tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>≤10 years</td>
<td>6/7</td>
<td>5/7</td>
</tr>
<tr>
<td>11–12 years</td>
<td>8/11</td>
<td>8/13</td>
</tr>
<tr>
<td>13–14 years</td>
<td>26/35</td>
<td>14/26</td>
</tr>
<tr>
<td>15–16 years</td>
<td>42/49</td>
<td>38/50</td>
</tr>
<tr>
<td>≥17 years</td>
<td>35/42</td>
<td>33/39</td>
</tr>
<tr>
<td>Total</td>
<td>117 (81%)</td>
<td>98 (73%)</td>
</tr>
</tbody>
</table>

**Table 2: Tuberculosis diagnosis by type and age in each group**

<table>
<thead>
<tr>
<th>All types of tuberculosis</th>
<th>Pulmonary tuberculosis</th>
<th>Non-pulmonary tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=279 (95% CI)</td>
<td>n=215</td>
<td>n=64</td>
</tr>
<tr>
<td>Both cities n=279</td>
<td>9% (-16 to 29)</td>
<td>-1% (-24 to 18)</td>
</tr>
<tr>
<td>Salvador n=183</td>
<td>11% (-20 to 34)</td>
<td>10% (-45 to 29)</td>
</tr>
<tr>
<td>Manaus n=96</td>
<td>-2% (-546 to 32)</td>
<td>-30% (-108 to 19)</td>
</tr>
</tbody>
</table>

**Table 3: Efficacy of revaccination against tuberculosis by tuberculosis type and city, controlled for age.**

Rodrigues et al Lancet 2005
Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi

*Karonga Prevention Trial Group*

“No evidence that any of the trial vaccines contributed to protection against tuberculosis”
Why the difference?

• Different endpoint
• Different population
• Difference may be real
BCG revaccination boosts Th1, Th17 and BCG-reactive NK cells

Suliman et al, 2016

Rakshit et al, 2019
Mucosal BCG protects better against low dose *M. tb* infection than intradermal BCG in NHPs

Dijkman et al NM 2019
IV BCG profoundly alters the outcome of M. tb infection in NHPs

Sharpe et al, 2016

Darrah et al, 2020
Infant BCG reduces non tuberculous infections in first 6 weeks

Prentice et al, The Lancet 2021
What do we still not know

• Immunological mechanisms of protection
  • Against infection
  • Against disease
  • With IV BCG

• Which antigens are protective
  • Unbiased identification of novel protective antigens

• How to quantify NTM exposure
IV BCG in mice expands HSCs and induces epigenetic changes in macrophages that are protective *in vivo*

Kaufmann et al, Cell 2018
Next generation BCG vaccines

• VPM1002
  • Phase III RCT in infants in Gabon, Kenya, South Africa, Tanzania and Uganda
  • Primary Endpoint: QFT conversion
  • Secondary Endpoint: TB disease
  • n ~7000

• MTBVAC
  • Phase IIa in newborns ongoing
  • Phase III to start Q4 2021 / Q1 2022
Summary

• 100 years on, there is still much we do not understand about BCG
  • Despite > 4.2bn doses administered
• But still a lot we can learn
• Parallel animal and human experimental medicine studies can be very informative
• BCG replacement vaccines now in late stage development
  • Need to be superior for efficacy and/or safety
  • Need also to be non-inferior for non-specific effects
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