Prevention of infection with *Mycobacterium tuberculosis* by H4:IC31 vaccination or BCG revaccination in healthy adolescents: results of a randomized controlled trial (NCT02075203)

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Background & Rationale

Lack validated preclinical models, immune correlates of vaccine-mediated protection

Prevention of TB disease (POD) efficacy trials large, long and costly

Primary BCG vaccination partial protection (19%) against *M.tb* infection

Roy BMJ 2014

**Can (re)vaccination prevent *M.tb* infection in a high transmission setting?**

- *M.tb* infection >10-fold frequency TB disease
- Prevention of Infection (POI) trial shorter, smaller, less costly vs POD

Hawn MMBR 2014

**Can POI trials be used as a decision-making tool for TB vaccine development?**

- candidate vaccine up/down selection
- trigger expansion POD efficacy trials

Ellis Tuberculosis 2015
Background & Rationale

Acquisition, persistence and clearance of *M.tb* infection cannot be measured directly

Interferon-gamma release assays (IGRA) = indirect measure of immune sensitization to *M.tb*

IGRA more specific than TST

*Pai Clin Microbiol Rev 2014*

IGRA conversion negative $\rightarrow$ positive $\approx$ increased risk TB disease

*Andrews AJRCCM 2015*

Human, animal studies TST reversion positive $\rightarrow$ negative $\approx$ decreased risk of TB disease

*Hawn MMBR 2014, Dharmadhikari Tuberculosis 2011*

Clinical significance of IGRA reversion unclear

*Andrews AJRCCM 2012*

Sustained IGRA conversion more likely associated with sustained *M.tb* infection, increased risk TB disease, than transient IGRA conversion with reversion
Background & Rationale

Aimed to evaluate safety, immunogenicity, and prevention of initial and sustained QuantiFERON-TB Gold In-tube (QFT) conversion by H4:IC31® or BCG revaccination in healthy South African adolescents in a high TB transmission setting

Demonstration of efficacy

→ seek immune correlates of protection against *M.tb* infection
→ utility of POI design for up/down selection of TB vaccine candidates
→ impetus for larger trials to test POD vaccine efficacy in *M.tb*-uninfected populations

Proviso:

2 previous large randomized trials: no overall benefit of BCG revaccination for POD

Did not screen *M.tb* infection status or measure acquisition

33% efficacy in subset of Brazilian children 7-11 years

*Rodrigues Lancet 2005*
*Barreto Vaccine 2011*
*Karonga PTG Lancet 1996*
Trial Design

Randomized, placebo-controlled, partially-blinded
990 healthy, HIV-uninfected, QFT-negative, adolescents (12-17 years)
BCG vaccinated in infancy
Excluded: Previous TB disease, household TB contact
2 sites (SATVI, Worcester; Desmond Tutu HIV Centre, Cape Town)

3 arms, randomized 1:1:1
Double-blind intramuscular injection (D0 and D56)
    Saline placebo
    OR
    H4:IC31® (15μg H4:500nmol IC31®)
    OR
Open-label intradermal injection (D0)
    BCG Vaccine (Statens Serum Institut) (2-8 x 10⁵ CFU)

H4 (Sanofi Pasteur) subunit vaccine (mycobacterial antigens Ag85B, TB10.4)
IC31® adjuvant (Valneva)
H4:IC31® protection in pre-clinical models, safe and immunogenic in humans

Billeskov PLoS ONE 2012
Geldenhuys Vaccine 2015
Norrby Vaccine 2017
Trial Design

First cohort (n=90) additional immunogenicity

Follow-up contingent on QFT status D84 and M6, 12, 18 and 24
QFT+ D84 ‘washout’ period excluded
QFT+ M6, 12, 18, 24 returned 3, 6 months later; and EoS

South African national guidelines
Do not recommend IPT for HIV-negative *M. tb*-infected persons >5 years old
(high risk of reinfection)
Preventive therapy not provided - QFT converters
Outcome Measures

**Safety Outcomes**
- All participants ≥1 injection
- Solicited AE 7 days, unsolicited AE and injection site AE 28 days (placebo/H4:IC31®) or 84 days (BCG), SAE and AESI to EoS

**Immunogenicity Outcomes**
- Safety & immunogenicity cohort
- Intracellular cytokine staining (ICS) and flow cytometry

**Efficacy Outcomes**
- Analyzed mITT population, received ≥1 injection and QFT- D84
- Exploratory analyses ITT and PP population

**Primary efficacy endpoint:**
- Initial QFT conversion (IFNγ ≥0.35 IU)/mL post-D84

**Secondary efficacy endpoint:**
- Sustained QFT conversion through 6 months after (post-D84) QFT conversion

**Exploratory efficacy endpoints:**
- Sustained QFT conversion through EoS
- Alternative thresholds - initial/sustained QFT conversion
Statistical Considerations

Distinguish 50% rate reduction initial QFT conversion H4:IC31® or BCG vs placebo

- 80% power, 10% one-sided Type 1 error rate
- Prioritize detection proof-of-concept signal (at expense of possible False+)

Not powered to distinguish POI efficacy H4:IC31® vs BCG
Not powered to distinguish POD efficacy

Sample size (330/arm) expected → 64 initial QFT conversion endpoints

Efficacy estimates based on Hazard Ratios (Cox regression model)

Primary, secondary efficacy analyzed using log-rank tests, H4:IC31® or BCG versus placebo,

Report both –

- 80% confidence intervals (pre-specified significance criteria)
- 95% confidence intervals (traditional significance criteria)
Results

Screening April 2014

<table>
<thead>
<tr>
<th>Screened (n=2976)</th>
<th>Excluded (n=1986)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QFT(+) (n=1405)</td>
</tr>
<tr>
<td></td>
<td>Not meeting other inclusion criteria (n=469)</td>
</tr>
<tr>
<td></td>
<td>Withdrew assent/consent (n=27)</td>
</tr>
<tr>
<td></td>
<td>Other reasons (n=85)</td>
</tr>
</tbody>
</table>

Randomized (n=990)

Allocated to placebo (n=329)  
ITT set

Allocated to H4:IC31 (n=331)  
ITT set

Allocated to BCG (n=330)  
ITT set

Safety analysis set (n=329)

QFT(+) or missing at Day 84 (n=19)
Safety follow up only

QFT(-) at Day 84 (n=310)
mlTT analysis set
Immunogenicity analysis subset (n=27)

Second injection given out of window (n=4)
PP analysis set (n=306)

Did not receive at least one injection (n=1)

Safety analysis set (n=330)

QFT(+) or missing at Day 84 (n=22)
Safety follow up only

QFT(-) at Day 84 (n=308)
mlTT analysis set
Immunogenicity analysis subset (n=28)

Second injection not given (n=2) or given out of window (n=9)
PP analysis set (n=297)

Safety analysis set (n=330)

QFT(+) or missing at Day 84 (n=18)
Safety follow up only

QFT(-) at Day 84 (n=312)
mlTT analysis set
Immunogenicity analysis subset (n=28)

PP analysis set (n=312)

LPLV August 2017

Loss to follow-up 4% (41/990) through EoS
Results: Baseline characteristics did not differ between arms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistic</th>
<th>Placebo (n=329)</th>
<th>H4:IC31® (n=330)</th>
<th>BCG (n=330)</th>
<th>Total (n=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>SATVI n (%)</td>
<td>306 (93.0)</td>
<td>306 (92.7)</td>
<td>305 (92.4)</td>
<td>917 (92.7)</td>
</tr>
<tr>
<td></td>
<td>DTHC n (%)</td>
<td>23 (7.0)</td>
<td>24 (7.3)</td>
<td>25 (7.6)</td>
<td>72 (7.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median (min, max)</td>
<td>14 (12, 17)</td>
<td>14 (12, 17)</td>
<td>14 (12, 17)</td>
<td>14 (12, 17)</td>
</tr>
<tr>
<td>Self-declared Race</td>
<td>Asian n (%)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Black African</td>
<td>120 (36.5)</td>
<td>120 (36.4)</td>
<td>126 (38.2)</td>
<td>366 (37.0)</td>
</tr>
<tr>
<td></td>
<td>Caucasian n (%)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>3 (0.9)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Cape Mixed Ancestry n (%)</td>
<td>207 (62.9)</td>
<td>208 (63.0)</td>
<td>200 (60.6)</td>
<td>615 (62.2)</td>
</tr>
<tr>
<td>Sex (females)</td>
<td>n (%)</td>
<td>169 (51.4)</td>
<td>189 (57.3)</td>
<td>162 (49.1)</td>
<td>520 (52.6)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Median (min, max)</td>
<td>19.9 (14.3, 36.8)</td>
<td>19.6 (13.8, 38.3)</td>
<td>19.4 (13.1, 36.9)</td>
<td>19.6 (13.1, 38.3)</td>
</tr>
</tbody>
</table>
Results: Safety

**Both vaccines - acceptable safety profile**

550 participants ≥1 AE

- H4:IC31® and placebo similar AE profile
- AE more frequent BCG arm (injection site AE, mild-moderate severity)
- Upper respiratory tract infection less frequent BCG vs placebo and H4:IC31 (2.1%, 7.9%, and 9.4%, respectively; p<0.001)

In total:
- 4 severe AE, 19 SAE
- No AESI or related severe AE or related SAE
- 1 death (suicide; placebo arm)

No difference in rate of severe AE or SAE between study arms

**No cases of active TB disease were observed**
Results: Immunogenicity

High baseline BCG responses
Both H4:IC31 and BCG were immunogenic
Results: Primary efficacy endpoint: Initial QFT Conversion

Total 134 initial QFT conversions (14.4%) = incidence 9.9 per 100 person-years

Placebo 15.8%

H4:IC31 14.3%

BCG 13.1%
Results: Primary efficacy endpoint: Initial QFT Conversion

Placebo 15.8%

H4:IC31 14.3%  VE 9.4%  (80% CI -18.3; 30.6)  (95% CI -36.2; 39.7)

BCG 13.1%  VE 20.1%  (80% CI -4.8; 39.1)  (95% CI -21.0; 47.2)

*Note: Very few participants remaining on study after M24
Results: Secondary Efficacy Endpoint: Sustained QFT Conversion

82 sustained QFT converters (8.8% of all participants; 62.6% of initial QFT converters)

- **Placebo**: 36/310 11.6%
- **H4:IC31**: 25/308 8.1%
- **BCG**: 21/312

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**IFN (IU/mL)**

**QFT conversion month**
Results: QFT Reversion

High QFT reversion rate (37.6%)

Placebo  12/48  (25.0%)

H4:IC31  17/42  (40.5%)

BCG  18/39  (46.2%)
Results: Secondary efficacy endpoint: Sustained QFT Conversion

<table>
<thead>
<tr>
<th>Group</th>
<th>Conversion Rate</th>
<th>VE</th>
<th>80% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4:IC31</td>
<td>8.1%</td>
<td>30.5%</td>
<td>(3.0; 50.2)</td>
</tr>
<tr>
<td>BCG</td>
<td>6.7%</td>
<td>45.4%</td>
<td>(22.3; 61.6)</td>
</tr>
</tbody>
</table>

![Graph showing time to sustained QFT conversion](image-url)
Results: Secondary efficacy endpoint: Sustained QFT Conversion

<table>
<thead>
<tr>
<th>Group</th>
<th>Sustained QFT Conversion (%)</th>
<th>80% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>(11.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4:IC31</td>
<td>(8.1%) VE 30.5%</td>
<td>(3.0; 50.2)</td>
<td>(-15.8; 58.3)</td>
</tr>
<tr>
<td>BCG</td>
<td>(6.7%) VE 45.4%</td>
<td>(22.3; 61.6)</td>
<td>(6.4; 68.1)</td>
</tr>
</tbody>
</table>

Participants with sustained QFT conversion (%)

Time to sustained QFT conversion (Months)

At Risk |
---------|
Placebo  | 310
         | 308
         | 312
H4:IC31  | 302
         | 303
         | 310
BCG      | 287
         | 288
         | 297

Placebo
H4:IC31
BCG
## Results: Exploratory efficacy endpoints

<table>
<thead>
<tr>
<th></th>
<th>Sustained QFT conversion EoS (≥0.35IU/mL)</th>
<th>Sustained QFT conversion (&lt;0.2 to &gt;0.7IU/mL)</th>
<th>Initial QFT conversion (&gt;4IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 11.6%</td>
<td>Placebo 10.0%</td>
<td>Placebo 10.6%</td>
</tr>
<tr>
<td></td>
<td>H4:IC31 7.8% VE 34.2% (80% CI 7.7; 53.0)</td>
<td>H4:IC31 7.8% VE 23.2% (80% CI -8.8; 45.8)</td>
<td>H4:IC31 7.1% VE 34.5% (80% CI 6.8; 54.2)</td>
</tr>
<tr>
<td></td>
<td>BCG 6.4% VE 48.2% (80% CI 25.9; 63.8)</td>
<td>BCG 6.1% VE 41.6% (80% CI 15.2; 59.8)</td>
<td>BCG 6.1% VE 45.1% (80% CI 20.5; 62.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI -10.4; 60.7)</td>
<td>(95% CI -3.3; 67.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI 10.5; 70.0)</td>
<td>(95% CI 3.8; 69.3)</td>
</tr>
</tbody>
</table>
Summary 1

Both H4:IC31 and BCG safe and immunogenic

Neither H4:IC31® nor BCG revaccination prevented initial QFT conversion

Vaccination can reduce rate of sustained QFT conversion in high TB transmission setting

Secondary endpoint: Sustained QFT conversion

*Modest signal H4:IC31® (VE 30.5%; 80% confidence 3 – 50%)*

- met pre-defined significance criteria for POI proof-of-concept
- did not meet conventional criteria for statistical significance

*Convincing efficacy signal BCG (VE 45.4%; 95% confidence 6 – 68%)*

- met traditional significance criteria for Phase 2b trials
Possible explanations consistent with the results

1) No reduction in rate initial QFT conversion (primary endpoint)
   - vaccination did not avert initial colonization, or antigen trafficking to lymphoid tissues to trigger adaptive immunity

2) Reduction in rate initial QFT conversion >4 IU/mL (exploratory endpoint)
   - vaccine-mediated reduction in bacterial replication following initial infection

3) Reduction in rate sustained QFT conversion (secondary endpoint)
   - vaccine-mediated QFT reversion associated with enhanced bacterial control or even clearance

Billeskov Plos one 2012
Impact and next steps...

1) *Evidence POI design can detect vaccine efficacy in high M.tb transmission setting*
   - identified sustained QFT conversion as suitable endpoint
   - cannot confirm utility of initial QFT conversion*
   - POI needs validation as tool for vaccine up-selection in future POD trial

2) *Modest H4:IC31 signal, suggests biological effect*
   - first indication of protection against *M.tb* in humans by novel subunit vaccine
   - impetus for development of related subunit vaccines

3) *Convincing BCG efficacy signal*
   - allow search for immune correlates of protection
   - justifies (re)evaluation of BCG revaccination for POD in *M.tb*-uninfected persons

* ≥0.35IU/mL threshold
Thanks to:

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The C-040-404 Study Team

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