Safety of a Typhoid Conjugate Vaccine Booster Dose in Malawian Children

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Blantyre Malaria Project

05 December 2023
# Main efficacy study design Malawi

<table>
<thead>
<tr>
<th>Site</th>
<th>Design</th>
<th>Control vaccine</th>
<th>Study duration</th>
<th>Number vaccinated</th>
<th>*AEFI cohort</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi</td>
<td>Individually randomized</td>
<td>Group A meningococcal vaccine</td>
<td>Feb 2018 – Sep 2022</td>
<td>28,130</td>
<td>602</td>
<td>9 months – 12 years</td>
</tr>
</tbody>
</table>

*Sub-study of 602 age-stratified children.


*AEFI: adverse events following immunization*
Efficacy against blood-culture confirmed S Typhi by age at vaccination, ITT analysis – 48-52 months

Comparatively lower efficacy in younger children – not statistically significant.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;2</th>
<th>2-&lt;5</th>
<th>5 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCV</td>
<td>Men-A</td>
<td>TCV</td>
</tr>
<tr>
<td>N</td>
<td>1555</td>
<td>1600</td>
<td>3503</td>
</tr>
<tr>
<td>S Typhi cases</td>
<td>4</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Incidence per 100,000 person-years (95% CI)</td>
<td>61 (23, 162)</td>
<td>207 (122, 349)</td>
<td>33 (14, 80)</td>
</tr>
<tr>
<td>Vaccine efficacy (95% CI)</td>
<td>70.6% (6.4%, 93.0%)</td>
<td>79.6% (45.8%, 93.9%)</td>
<td>79.3% (63.5%, 89.0%)</td>
</tr>
</tbody>
</table>

Patel PDP et al. Efficacy of Typhoid Conjugate Vaccine: Final Analysis of a Four-Year, Randomised Controlled Trial in Malawian Children. SSRN 2023.
24 to 34 months of safety and immunogenicity follow-up published in Lancet Global Health 2022

Safe, tolerable, and immunogenic up to 730–1035 days post-vaccination
Anti-Vi immunoglobulin G antibody immunogenicity by age at vaccination, PP analysis – 24-34 months

Trend toward faster waning of antibody over time in younger children – not statistically significant

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>TCV</th>
<th></th>
<th>Men-A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seroconversion % (95% CI)</td>
<td>Seroconversion % (95% CI)</td>
<td>Seroconversion % (95% CI)</td>
<td>Seroconversion % (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Day 0 to day 28</td>
<td>Day 0 to day 1035</td>
<td>Day 0 to day 28</td>
<td>Day 0 to day 1035</td>
</tr>
<tr>
<td>All</td>
<td>98.6 (96.4-99.5)</td>
<td>79.9 (74.1-84.7)</td>
<td>0.4 (0.1-2.1))</td>
<td>4.4 (2.4-8.2)</td>
</tr>
<tr>
<td>9-11 months</td>
<td>99.0 (94.4 - 99.8)</td>
<td>68.3 (55.8 - 78.7)</td>
<td>0.0 (0.0 - 4.4)</td>
<td>1.9 (0.3 - 9.9)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>97.8 (92.3 - 99.4)</td>
<td>78.4 (67.7 - 86.2)</td>
<td>1.1 (0.2 - 5.7)</td>
<td>4.1 (1.4-11.3)</td>
</tr>
<tr>
<td>6-12 years</td>
<td>99.0 (94.3 - 99.8)</td>
<td>89.4 (81.1. - 94.3)</td>
<td>0.0 (0.0 - 4.1)</td>
<td>6.6 (2.8 - 14.5)</td>
</tr>
</tbody>
</table>

Rationale for booster study

WHO research priority: Need for a booster dose?

- Single dose TCV is efficacious for >4 years in all age groups.
- However, the youngest age group has a trend toward:
  - Lower point estimate of efficacy at 4 years (NOT statistically significant)
  - Quicker waning of immunogenicity over time (NOT statistically significant)
- But...
  - Will continue to be exposed to S Typhi throughout childhood, and into adulthood
  - Target for routine immunization is 9 months in Malawi
- Therefore...
  - Malawi cohort provides a unique opportunity to evaluate the performance of a booster dose of TCV at about 5 years following original dose (school-age booster).
Booster study methodology

• Study design: Open label.

• Study population: Children in Malawi efficacy trial vaccinated with study vaccines between 9-11 months of age.

• Objective: in children who received the Men-A or TCV at 9-11 months of age,
  • Determine **immunogenicity** to a dose of TCV given at 5 years of age.
    • Serum anti-Vi IgG antibodies pre-vaccination, at 28 days (Day 28) and 120-180 days (Day 160) post vaccination.

• Determine **safety profile** of a second TCV given at 5 years of age.
  • Local and systemic solicited AEs within 7 days after vaccination.
  • Local and systemic unsolicited AEs within 28 days after vaccination.
  • SAEs within 180 days after vaccination.

• Determine **tetanus antibody response** to a dose of Vi-TCV at 5 years of age.
Malawi trial consort diagram

29,949 Screened
28,217 Eligible
28,212 Randomized

14,069 ITT (TCV)
14,061 ITT (Men-A)
13,945 PP (TCV)
13,937 PP (Men-A)

72 aged 9-11 months at first vaccination enrolled in booster (Booster TCV)
64 aged 9-11 months at first vaccination enrolled in booster (1ST TCV)
Local adverse events at day 7 post-vaccination

- Similar rate in both arms - p-value 1.0
- Mostly mild and moderate
- All reactions resolved by day 5 post-vaccination
Systemic adverse events at day 7 post-vaccination

- Similar rate in both arms - p-value 0.27
- Mostly mild and moderate
- Fever persisted to day 7 for one participant in each arm
Conclusions

- First study to document TCV booster dose safety in African children.
- TCV caused few AEs after first or booster dose.
  - Mostly mild and moderate.
- Tolerability of first and booster doses of TCV at age 5 years was similar.
- Data support TCV introduction into routine immunization schedules in similar settings.
Acknowledgements

Blantyre Malaria Project
• Nginache Nampota
• Victoria Mapemba
• Newton Selemani

CVD, University of Maryland
• Kathy Neuzil
• Matt Laurens
• Shrimati Datta
• Tamar Pair
• Leslie Jamka
• Yuanyuan Liang
• Pasetti Lab

Malawi Liverpool Wellcome Trust
• Melita Gordon
• Robert Heyderman
• Theresa Misiri
• Felistas Kumwenda
• James Meiring
• Pratiksha Patel
• Priyanka Patel
• Richard Wachepa
• Nedson Chasweka
• Happy Banda
• Mark Haward
• Alfred Muyaya

Children and their parents
Funded by the Bill & Melinda Gates Foundation
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http://takeontyphoid.org