Longer-term efficacy of typhoid conjugate vaccine in Malawi

Dr. Priyanka D. Patel
Malawi Liverpool Wellcome Programme
13th International Conference on Typhoid & Other Invasive Salmonelloses
Typhoid cases - Malawi

High incidence of MDR typhoid 2016-2019 (STRATAA) *444/100,000 PYO

*Meiring et al, Lancet 2021
# TyVAC trial of TCV: Study design and objectives

<table>
<thead>
<tr>
<th>Design</th>
<th>Typhoid conjugate vaccine (TCV)</th>
<th>Control vaccine</th>
<th>Study dates</th>
<th>Target no. vaccinated</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individually randomized</td>
<td>Typbar™ TCV (Bharat Biotech)</td>
<td>Group A meningococcal vaccine (MenA)</td>
<td>Feb 2018 – Sep 2022</td>
<td>28,000 1:1 ratio</td>
<td>9 months – 12 years</td>
</tr>
</tbody>
</table>

*Sub-study of 600 age-stratified children.

**Primary objective**
- **Vaccine efficacy**: Blood-culture confirmed typhoid incidence, TCV vs MenA
- **48-month final analysis**: Data lock Sept 30, 2022

**Secondary and exploratory objectives**
- Safety, tolerability, and immunogenicity
- **Durability, age-band efficacy**


Consort diagram

29,949 Screened

28,217 Eligible

28,212 Randomized

14,069 ITT (TCV)

13,945 PP (TCV)

14,061 ITT (MenA)

13,937 PP (MenA)
Typhoid vaccine trial results @18-24 months

*Safe & immunogenic

**80.7% efficacious @ 18-24 months

*Co-administration (Measles Rubella)

Durability of protection

Efficacy in youngest children

**Patel et al, NEJM 2021 (Malawi).
## Passive surveillance data, 48-month analysis

<table>
<thead>
<tr>
<th>Enhanced passive surveillance for typhoid</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened passive surveillance visits</td>
<td>39,174</td>
</tr>
<tr>
<td>Eligible ($T \geq 38^\circ$ or 3 days reported fever)</td>
<td>10,777</td>
</tr>
<tr>
<td>Blood cultures collected (96% of fever)</td>
<td>10,136</td>
</tr>
<tr>
<td>Typhoid cases (1.3% of cultures)</td>
<td>136</td>
</tr>
<tr>
<td>*SAEs (all deemed unrelated to vaccine)</td>
<td>554</td>
</tr>
<tr>
<td>Deaths (one typhoid death (MenA group))</td>
<td>34</td>
</tr>
</tbody>
</table>

Map of Blantyre showing vaccine coverage (orange dots) and typhoid cases (blue dots) among vaccinated children.
Blood cultures and typhoid cases over time

**MenA**

- Typhoid case
- Blood culture taken

**TCV**

- Typhoid case
- Blood cultures taken

[Graph showing blood cultures and typhoid cases over time for MenA and TCV]
**Vaccine Efficacy: 78.3% (95% CI: 66.3% - 86.1%)**

**No. Needed to Vaccinate: 163 (95% CI: 129 - 222)**

*Final ITT analysis – 48-52 months follow-up*

<table>
<thead>
<tr>
<th>28,130 children</th>
<th>TCV</th>
<th>MenA</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months – 12 years</td>
<td>n=14,069</td>
<td>n=14,061</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up time</th>
<th>person-years</th>
<th>60,500</th>
<th>60,220</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Typhoid cases</th>
<th>culture positive</th>
<th>24</th>
<th>110</th>
</tr>
</thead>
</table>

| Incidence /100,000 pyo (95%CI) | 39.7 (25.4, 59) | 182.7 (150.1, 220.2) |

110 typhoid cases in MenA arm
24 typhoid cases in TCV arm

Kaplan Meier for ITT population

Maximum number at risk
MenA: 14061 14035 14066 13982 13976 13971 13929 13907 13893 1616
TCV: 14069 14067 14060 14045 14043 14041 13996 13985 13980 1655

p<0.001
Meta-regression of vaccine efficacy over 5 annual intervals

Vaccine efficacy estimated to fall by 1.3% per annum

Slope [95% CI] = -0.013 [-0.098, 0.072], p=0.77

Weights: Inverse-variance
### Efficacy by age at vaccination

<table>
<thead>
<tr>
<th>Age Group</th>
<th>TCV</th>
<th>MenA</th>
<th>TCV</th>
<th>MenA</th>
<th>TCV</th>
<th>MenA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2y</td>
<td>1555</td>
<td>1600</td>
<td>3503</td>
<td>3579</td>
<td>9011</td>
<td>8882</td>
</tr>
<tr>
<td>Typhoid cases</td>
<td>4</td>
<td>14</td>
<td>5</td>
<td>25</td>
<td>15</td>
<td>71</td>
</tr>
<tr>
<td>Incidence (per 100,000 PYO)</td>
<td>60.7 (22.8, 161.8)</td>
<td>206.7 (122.4, 349.0)</td>
<td>33.3 (13.9, 80.1)</td>
<td>163.4 (110.4, 241.9)</td>
<td>38.6 (23.2, 64.0)</td>
<td>186.1 (147.5, 234.8)</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td><strong>70.6% [6.4%, 93%]</strong></td>
<td><strong>79.6% [45.8%, 93.9%]</strong></td>
<td><strong>79.3% [63.5%, 89.0%]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- Safe & immunogenic
- 78.3% efficacious @ 4+ years
- Co-administration (MR)
- *Durability of protection
- *Efficacy in youngest children

Challenges

- Infrastructure damage (Cyclone Freddy)
- Vaccinator fatigue (COVID, cholera, polio)
- Community fatigue
**Aims:**

**Effectiveness** – case control study, test-negative design.

**Impact** – ecological, proportionate reduction in typhoid incidence before and after.

---

**MITIMA Measuring the Effectiveness and Impact of TCV Introduction in Malawi**

Fever → blood culture

9mo – 15 years (vaccine eligible)
- Not typhoid
- Typhoid

16-45 years (not vaccinated)
- Not Typhoid
- Typhoid

**Compare positive vs. negative**

**Effectiveness**

**Compare before vs. after**

**Impact**
The Typhoid Vaccine Acceleration Consortium (TyVAC) is led by the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH. TyVAC is funded by the Bill & Melinda Gates Foundation.
TyVAC works closely with global partners
Acknowledgements

Study participants and their communities

MLW TyVAC teams
MLW core support
Kathy Neuzil & UMB TyVAC team

Funded by: Bill & Melinda Gates Foundation
Supplementary