Overview of typhoid conjugate vaccine pipeline: current status and future plans

Sushant Sahastrabuddhe
10th Typhoid Conference, Kampala, Uganda
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Outline of Presentation

- Currently available typhoid vaccines
- Typhoid conjugate vaccines:
  - US NIH Vi-rEPA
  - Bharat Vi-TT
  - Biomed Vi-TT
  - Zydus Vi-TT
  - Vi-CRM
  - IVI Vi-DT partners
- Candidate pipeline and status
- Path forward and issues
## Typhoid vaccines currently recommended by WHO

<table>
<thead>
<tr>
<th></th>
<th>Vi polysaccharide vaccine (ViPS)</th>
<th>Ty21a vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of vaccine</strong></td>
<td>Subunit</td>
<td>Live attenuated</td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td>Purified Vi capsular polysaccharide (Ty2 S. Typhi strain)</td>
<td>Ty2 S. Typhi strain with chemically mutated genes</td>
</tr>
<tr>
<td><strong>Route, Dose</strong></td>
<td>IM 1 dose</td>
<td>Oral, 3-4 doses</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Liquid (25 ug Vi antigen in buffer solution per one dose of 0.5ml)</td>
<td>Capsule</td>
</tr>
<tr>
<td><strong>Min. age of vaccination</strong></td>
<td>2 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>55-72%</td>
<td>33-67%</td>
</tr>
<tr>
<td><strong>Duration of protection</strong></td>
<td>3 yrs</td>
<td>7 yrs</td>
</tr>
<tr>
<td><strong>Safety/tolerability</strong></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>PQ</strong></td>
<td>Typhim Vi (2011)</td>
<td>No</td>
</tr>
</tbody>
</table>
Newer Typhoid Vaccines: subunit approach

Issues with polysaccharide:
- T-cell independent: Poorly immunogenic in young children, No booster response
- Requires repeat dosing every 3 years
- Modestly immunogenic (55% at the end of 3 years)

Conjugation:
A process wherein a poorly immunogenic molecule (polysaccharide) is covalently bound to a carrier protein thereby increasing the immunogenicity of the final product and making it T-cell dependent.
Currently available polysaccharide-protein conjugate vaccines

• Pneumococcal vaccine:
  - Prevnar®
  - Synflorix®
  - Prevnar 13®

• Haemophilus influenzae type B vaccine:
  - ActHIB®
  - Hiberix®
  - PedvaxHIB®
  - All pentavalent vaccines have Hib conjugate

• Meningococcal vaccine:
  - Menveo®
  - Menactra®
  - Menafrivac®

• Typhoid vaccine:
  - Pedatypy®
  - Typbar-TCV®
Developed by US NIH (John Robbins and colleagues)
Capsular polysaccharide of *Salmonella typhi* (Vi) was bound to the recombinant exoprotein A (rEPA) of *Pseudomonas aeruginosa*
Have completed clinical evaluation in humans including in the target group (Infants)
Proposed serologic correlates of protection (2 ug/ml) in 2-5 years old efficacy study
Vi-rEPA clinical trials

Phase I and II
- Safety and immunogenicity in adults, teenagers, and 2-4 year olds (Kossaczka 1999)
- 382 participants; 2 doses of Vi-rEPA1 and Vi-rEPA2

Phase III
- Efficacy in 2 to 5 years old (Lin et al 2001)
- 12,008 children (at least 1 dose); 91% efficacy (89 at the end of 4 years)

Dose-ranging
- Dose (5, 12.5, 25 µg of Vi) study in 2-5 years old (Canh et al 2004)
- 241 children, 2 injections 6 weeks apart for all three doses; dose-related response observed, 25 was recommended for > 2 while for < 2, 12.5 and 25 were tested

Infant
- Concomitant administration with routine infant vaccines (Thiem et al 2011)
- 318 infants, suppressive effect of high levels of maternally-derived IgG antibody was observed
### Efficacy of Vi-rEPA in 2-to-5 years old children who received 2 doses 6 weeks apart

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccine group</th>
<th>placebo group</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active surveillance (0 to 27 month)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of fully immunized</td>
<td>5525</td>
<td>5566</td>
<td></td>
</tr>
<tr>
<td>No. of typhoid cases</td>
<td>4</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Attack rate (cases/1000/yr)</td>
<td>0.60</td>
<td>7.04</td>
<td>91.5 (77.1-96.6)</td>
</tr>
<tr>
<td><strong>Passive surveillance (27 to 46 month)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. remaining in study</td>
<td>5383</td>
<td>5420</td>
<td></td>
</tr>
<tr>
<td>No. of typhoid cases</td>
<td>3</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Attack rate (cases/1000/yr)</td>
<td>0.362</td>
<td>2.34</td>
<td>82.4 (22.3-99.1)</td>
</tr>
<tr>
<td><strong>Active and Passive surveillance (0 to 46 month)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of typhoid cases</td>
<td>7</td>
<td>66</td>
<td>89.3 (76.0-96.9)</td>
</tr>
<tr>
<td>Attack rate (cases/1000/yr)</td>
<td>0.317</td>
<td>2.96</td>
<td></td>
</tr>
<tr>
<td><strong>Single dose (0 to 27 month)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=771)</td>
<td>1</td>
<td>8</td>
<td>87.7 (65.1-96.8)</td>
</tr>
</tbody>
</table>

Source: Dr Shousun Szu, NIH

Lin et al. The efficacy of a *Salmonella typhi* conjugate vaccine in two-to-five-year-old children. NEJM 2001;344:1263-1269
Vi-rEPA: Current status

- US NIH transferred the technology to Lanzhou Institute of Biological Products (LIBP), part of the China National Biologics Group (CNBG)

- LIBP conducted additional trials and have submitted for in-country licensure in China in 2013
Vi-TT (BBIL)

- **Controlled Trial**
  - 2-45 yrs
  - n = 654 randomised to 2 arms

- **Test Vaccine: Typbar-TCV™**
  - 25 μg/0.5 ml Vi capsular polysaccharide TT conjugate vaccine
  - Single dose, I.M injection.

- **Reference Vaccine: Typbar®**
  - 25 μg/0.5 ml Vi capsular polysaccharide vaccine.
  - Single dose, I.M injection.

- **Open Label Trial**
  - 6 m – 2 yrs
  - n = 32

- **Immunogenicity end-points**
  - geometric mean titers
  - 4-fold rise of anti-Vi IgG response 6 weeks post vaccination

Mohan VK et al., Clin Infect Dis. 2015; 61(3):393-402.
Approx 98% of children in both age groups seroconverted and achieved GMTs establishing protective levels of immunogenicity.

Antibody persistence: post single dose, children 6–23 mths had GMTs on day 720 >5-fold above baseline.

### Table 3. Serum Immunoglobulin G Vi Antibody Responses Among Infants and Toddlers 6–23 Months of Age in the Open-Label Trial at Day 42 After a Single Dose of Typhar-TCV Compared With Day 0

<table>
<thead>
<tr>
<th>Response</th>
<th>Time-point</th>
<th>6–23 mo</th>
<th>6–11 mo</th>
<th>12–23 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td></td>
<td>307</td>
<td>139</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>Day 720</td>
<td>220</td>
<td>105</td>
<td>115</td>
</tr>
<tr>
<td>% Seroconversion (95% CI) (&gt;4-fold rise over day 0 baseline)</td>
<td>Day 42</td>
<td>98.1% (95.7–99.2)</td>
<td>97.8% (93.6–99.5)</td>
<td>98.2% (94.6–99.6)</td>
</tr>
<tr>
<td></td>
<td>Day 720</td>
<td>59.5% (52.9–65.8)</td>
<td>59.0% (49.5–67.9)</td>
<td>60.0% (50.8–68.5)</td>
</tr>
<tr>
<td>GMT, EU/mL (95% CI)</td>
<td>Day 0</td>
<td>9.5 (8.7–10.3)</td>
<td>9.6 (8.4–10.9)</td>
<td>9.4 (8.3–10.5)</td>
</tr>
<tr>
<td></td>
<td>Day 42</td>
<td>1937.4 (1785–2103)</td>
<td>1850.6 (1628–2104)</td>
<td>2012.4 (1811–2236)</td>
</tr>
<tr>
<td></td>
<td>Day 720</td>
<td>48.3 (42–55)</td>
<td>45.3 (37–55)</td>
<td>50.9 (42–61)</td>
</tr>
<tr>
<td>Fold rise over baseline GMT</td>
<td>Day 42</td>
<td>205</td>
<td>193</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>Day 720</td>
<td>5.17</td>
<td>5.1</td>
<td>5.24</td>
</tr>
</tbody>
</table>

Anti-Vi immunoglobulin G antibody titers estimated by VaccZyme enzyme-linked immunosorbent assay kit.
Abbreviations: CI, confidence interval; EU, enzyme-linked immunosorbent assay units; GMT, geometric mean titer.
Typbar-TCV: Current status

- Licensed in India as a single dose vaccine 25ug in 2013
- BBIL has submitted the dossier for WHO PQ in 2016 and is currently under review
- BBIL is also conducting additional studies on Typbar-TCV:
  - Co-admin with measles-containing vaccine (completed)
  - Post marketing surveillance
  - Oxford Vaccine Group human challenge study (results presented yesterday)
Pedatyp™ Biomed vaccine.

- Licensed for more than 3 months of age in 2008 in India.
- Single dose of 0.5 ml, followed by booster at 2.5 to 3 years age

Clinical Study

- Safety and immunogenicity in 169 subjects > 12 weeks with a comparison group (Vi) of 37 children > 2 years
- Four fold or greater rise in antibody titer of each group on ELISA which was statistically equivalent to Vi-rEPA
Effectiveness trial completed in Kolkata with 2000 children (6m to 12 years) http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=4714&EncHid=&userName=Vi-TT

- 2 doses at 6 weeks interval in children 6 mths to 12 yrs
- Authors report 100% VE after 1 year of follow up
- No plans yet of WHO PQ application
Vi-TT (Zydus Cadila)

• Zydus cadila developed a typhoid conjugate vaccine using TT as the carrier protein
• Phase I was completed in India
• Phase II/III with non-inferiority with Typbar-TCV™ (238 participants in all age groups) completed at 7 sites in India
• After the non-inferiority study, dossier has been submitted to DCGI (Indian NRA) for marketing authorization in India
• Expected Marketing authorization: May 2017
• Single dose 25ug from 6 months of age onwards
Vi-CRM$_{197}$ (GVGH)

- Developed by GSK Vaccines Institute for Global Health (GVGH, formerly NVGH)
- Have used CRM$_{197}$ as carrier protein
- CRM$_{197}$ is a non-toxic mutant of diphtheria toxin

**Phase I**
- Safety and Immunogenicity of Vi-CRM$_{197}$ Vaccine Against S. Typhi in Adult (18-40 Years Old). Found safe and immunogenic
- Completed in Belgium, 50 participants

**Phase II**
- Safety and Immunogenicity of various Formulations (25, 12.5, 5, 1.25 µg) in Adults (18-40 Years Old).
- Completed in Belgium, 88 participants

**Phase II**
- Safety, Reactogenicity and Immunogenicity of Vi-CRM197 Vaccine Against S. Typhi in Adults, Children, Older Infants (9 to 12 months) and Infants (6 weeks)
- 320 participants, studies completed in India, Philippines, and Pakistan
\textbf{Vi-CRM}_{197} (GVGH)

- In summary,
  - Phase I and II in European adults $\rightarrow$ at least as immunogenic as ViPS \textit{(van Damme et al. PLoS One 2011)}
  - Phase II in adults, children and infants in India, Pakistan and the Philippines (coadmin: msls 9 m, pentavalent & OPV at 6, 10, 14 wks) \textit{(Bhutta et al. Lancet Infect Dis 2014)}
  - Anti-Vi IgG titers after 1 dose 5 $\mu$g Vi $\geq$ ViPS 25 $\mu$g (adults and children)
  - Immunogenic in 6-8 wk and 9-12 m infants (in latter, immune response equal or greater than 1 dose ViPS in children and adults).
  - 	extbf{Antibody titers short-lived (~ 6 m); apparent lack of booster response.}
  - Technology transferred to Biological E and undergoing full clinical development (Plan presented on the first day)
Vi-DT (IVI)

With the initial know-how from US NIH, IVI scientists developed the technology to adopt for developing country manufacturers.
Vi-DT: SK chemicals

• Technology transfer completed in 2013
• Preclinical studies completed in 2015
• Phase I clinical trial completed in the Philippines
  
  “A Randomized, Observer-Blinded, Phase I study to Assess the Safety and Immunogenicity of Vi-DT Conjugate Vaccine compared to Vi-Polysaccharide (Typhim Vi®, Sanofi Pasteur) Typhoid Vaccine in Healthy Filipino Adults and Children”

• Phase I results will be public in July 2017
• Phase II preparations ongoing (dose scheduling in <2 years of age group)
• Phase II planned to start in Q42017
Biofarma:
- Technology transfer completed in 2013
- Preclinical studies completed in 2015
- Phase I clinical trial to start in Jakarta, Indonesia in April 2017

Incepta:
- Technology transfer completed in 2014
- Scale-up has been done to 50 L scale and preclinical studies are planned to start soon
Typhoid conjugate vaccine pipeline

1994-2010

Preclinical stage  |  Phase I  |  Phase II  |  Phase III  | National licensure  | Phase 4 studies

- Biological E (B)
- PT Biofarma (A)
- Finlay Inst
- SK Chemicals (A)
- Incepta (A)
- EuBiologics
- DAVAC
- Walvax

(B) NVGH technology transfer

(A) IVI technology transfer

- Vi-CRM197
- Vi-DT
- Vi-TT
- Vi-rEPA
- Under review

BioMed (licensed 2008)

Bharat (licensed 2013)
Typhoid conjugate vaccines: Issues

• Correlates of protection are not clearly established and approved by WHO
• There is no clinical efficacy trial conducted in children younger than 2 years of age. Data from human challenge studies can supplement this.
• The ELISA methods used by developers and manufacturers are not standardized (work ongoing at NIBSC to develop standard serum)
• Lack of clarity on the number of doses in the primary series and need and timing of the booster dose
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Manufacturers
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• Biomed
• Zydus Cadila
• SK chemicals
• Biological E
• Lanzhou Institute of Biological Products
• PT Biofarma
• Incepta Vaccines Ltd
• Finlay Institute
• Walvax
• Eubiologics

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