(Typhoid Vi Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccine)

9th International Conference on Typhoid and invasive NTS Disease  30th April – 3rd May 2015

Vineeth Varanasi
Before the beginning: Typhoid vaccine development at BBIL

2000: *Salmonella typhi* Ty2 strain generously provided to BBIL by Dr. John Robbins, NIH. Development of Vi capsular polysaccharide vaccine (Typbar)

2002: Phase III study, multi center randomized, active controlled immunogenicity trial with 185 subjects comparing Typbar to Vactyph (Cadilla)

2003: Typbar licensure

2009-2010: Phase IV post-licensure, multi center, randomized, 534 subject comparator controlled non-inferiority study comparing Typbar to Typherix (GSK)
Typbar-TCV Development-Milestones

- **2005**: R&D scale Vi conjugation to TT
- **2006**: Studies at NIBSC & BBIL
  - Characterization of conjugate
  - Mouse immunogenicity
- **2007**: Non-clinical Toxicity
  - Stability testing
- **2010**: Phase II Clinical Trial
- **2012**: Phase III Clinical Trial
- **2013**: Licensure
- **2014 -** Post-Licensure studies

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- **2005**: TCV Measles Interference
- **2006**: Passive Surveillance
- **2010**: Active Surveillance
Selection of Conjugation Method

Method 1
Method 2
Method 3
Vi- Polysaccharide
Clinical Trial Phase-IIa/IIb

Open label active controlled Phase IIa / IIb study to evaluate the safety and immunogenicity of BBIL’s Typhoid VIPs – TT Conjugate Vaccine Vs Reference Typhoid Vi Capsular Polysaccharide Vaccine in healthy teenagers (17-13 yrs) and children (12–2 yrs old).

Protocol Number: BBIL/CTP/02/2008

- Number of subjects enrolled: 100
- Number of subjects who completed study and were analyzed: 95
Single dose of 25µg Typbar-TCV is as immunogenic as two separated doses of 25µg or 15µg Typbar-TCV.
# Typbar-TCV Product Characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Liquid Vaccine</td>
</tr>
<tr>
<td>Storage</td>
<td>5°C ± 3°C</td>
</tr>
<tr>
<td>Dose volume</td>
<td>0.5 ml (Intramuscular injection)</td>
</tr>
<tr>
<td>Shelf life</td>
<td>24 months @ 5°C ± 3°C</td>
</tr>
<tr>
<td>O-Acetyl content (Hestrin)</td>
<td>NLT 0.085 ± 25% (25 µg of Vi Polysaccharide)</td>
</tr>
<tr>
<td>Vi Content</td>
<td>NLT 25 µg of Vi Polysaccharide</td>
</tr>
<tr>
<td>Free Vi-PS</td>
<td>NMT 20%</td>
</tr>
</tbody>
</table>
A Phase III, randomized, multicentric, controlled study to evaluate the immunogenicity and safety of BBIL's Typhoid Vi Capsular Polysaccharide Tetanus Toxoid Protein Conjugate Vaccine (Typbar – TCV™) vs. Reference Vaccine (Typbar®) in healthy subjects.

CTRI Registration No : CTRI/2011/08/001957
Trial Initiation Date : 22nd August 2011
Trial Completion Date : 07th February 2012

Test Vaccine: Typbar-TCV™ (TCV); 25 µg/0.5 ml S.Typhi (Ty2) Vi capsular polysaccharide Tetanus Toxoid conjugate vaccine. Single dose, I.M injection.

Reference Vaccine: Typbar®; 25 µg/0.5 ml S.Typhi (Ty2) Vi capsular polysaccharide vaccine. Single dose, I.M injection.

Follow up: Safety and Immunogenicity Days 42, 90, 540, 720 and 762
Study objectives

- Comparative assessment of the immunogenicity of typhoid conjugate (TCV) with Vi polysaccharide (comparator).
  - Primary endpoint: anti-Vi IgG response, 6 wks post vaccination.
  - Evaluate safety of TCV across all age groups (6 months – 45 years).
- Long-term persistence of anti-Vi IgG.
- Booster responses
- Qualitative assessment of anti-VI response: Avidity, IgG subclasses.
Study investigators and sites

- Dr. Monjori Mitra, Institute of Child Health, Kolkata
- Dr. G. Sampath, Institute of Preventive Medicine, Hyderabad.
- Dr. P. Venugopal, King George Hospital, Visakhapatnam.
- Dr. Mukesh Gupta, Soumya Child Clinic, Jaipur
- Dr. Sudhakar, Priya Children’s Hospital, Vijayawada
- Dr. S.N. Mahantashetti, JNMC, Belgaum
- Dr. Sri Krishna, Mahavir Hospital, Hyderabad
- Dr. Bhuvaneswar Rao, Sri Srinivasa Children’s Hospital, Vijayawada

Study was conducted in highly endemic or endemic areas of India.
Expectations from typhoid vaccines

- Safe in all ages, including children.
- Immunogenic
  - High titre IgG response.
  - Immune response in children < 2 years.
- Persistence of Vi specific antibodies.
- Antibody avidity and IgG subclasses.
- Immunological memory - Booster response

WHO. ECBS Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines. 2013
Clinical Safety results

Fever
Pain at injection site
Swelling
Arthralgia
Tenderness
Myalgia
Febrile convulsion

Open Label Trial – TCV (n=332)

- 13
- 32 (10%)

Controlled Trial – TCV (n=332)

- 12
- 14

Controlled Trial – Typbar (n=305)

- 8
- 9

p=0.52
p=0.56
p=0.21
p=1.0

Typbar-TCV is safe in all age groups and is comparable to existing vaccines
High titre anti-Vi IgG response – 6 wks

Open Label Trial – TCV
Controlled Trial – TCV
Controlled Trial - Typbar

Typbar-TCV is significantly more immunogenic than Vi polysaccharide.
Vaccine lot consistency

High degree of lot-to-lot consistency of both single and multi-dose presentations

Graph showing Anti-Vi IgG (EU/ml) levels for different lots:
- 76CI10001 (n=169) Single Dose
- 76CI10002 (n=165) Single Dose
- 76CI10003 (n=169) Single Dose
- 76CJ11001 (n=46) Multi-Dose
- 76CJ11002 (n=46) Multi-Dose
- 76CJ11003 (n=45) Multi-Dose
Seroconversion

Open Label Trial – TCV
Controlled Trial – TCV
Controlled Trial - Typbar

% Seroconversion

Days after Immunization

p=0.01

p=0.001
# Antibody Persistence

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 42</th>
<th>Day 720</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typbar-TCV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Open Label Trial</strong></td>
<td>No. of subjects</td>
<td>307</td>
<td>307</td>
</tr>
<tr>
<td></td>
<td>GMT EU/ml (95% CI)</td>
<td>9.5 (9,10)</td>
<td>1937.4 (1785,2103)</td>
</tr>
<tr>
<td></td>
<td>Fold change</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td><strong>Controlled Trial</strong></td>
<td>No. of subjects</td>
<td>332</td>
<td>332</td>
</tr>
<tr>
<td></td>
<td>GMT EU/ml (95% CI)</td>
<td>10.4 (9.6,11.3)</td>
<td>1292.5 (1153,1449)</td>
</tr>
<tr>
<td></td>
<td>Fold change</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td><strong>Typbar</strong></td>
<td>No. of subjects</td>
<td>305</td>
<td>305</td>
</tr>
<tr>
<td></td>
<td>GMT EU/ml (95% CI)</td>
<td>11.6 (10.5,12.9)</td>
<td>411.1 (359,471)</td>
</tr>
<tr>
<td></td>
<td>Fold change</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>
Typbar-TCV is immunogenic in all age groups
Greater antibody persistence in older age groups (>15 years)
2 years after a single dose GMT rise over baseline in all ages is ≥ 5 fold
Comparative immunogenicity

Anti-Vi antibodies likely to persist over the protective level for up to 4 years after vaccination

# Booster responses – 2 years

## Open Label Trial

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 42</th>
<th>Day 720</th>
<th>Day 762 (42 days post booster)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typbar-TCV</strong></td>
<td></td>
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</tr>
<tr>
<td>No. of subjects</td>
<td>307</td>
<td>307</td>
<td>220</td>
<td>187</td>
</tr>
<tr>
<td>GMT EU/ml (95% CI)</td>
<td>9.5 (9,10)</td>
<td>1937.4 (1785,2103)</td>
<td>48.7 (43,56)</td>
<td>1721.9 (1503,1972)</td>
</tr>
<tr>
<td>Fold change</td>
<td>205</td>
<td>5.2</td>
<td>178</td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>

## Controlled Trial

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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>332</td>
<td>332</td>
<td>243</td>
<td>175</td>
</tr>
<tr>
<td>GMT EU/ml (95% CI)</td>
<td>10.4 (9.6,11.3)</td>
<td>1292.5 (1153,1449)</td>
<td>81.7 (73,92)</td>
<td>1685.3 (1468,1797)</td>
</tr>
<tr>
<td>Fold change</td>
<td>124</td>
<td>7.8</td>
<td>162</td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

## Typbar

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<tr>
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<th>Day 762 (42 days post booster)</th>
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</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>305</td>
<td>305</td>
<td>197</td>
<td>57</td>
</tr>
<tr>
<td>GMT EU/ml (95% CI)</td>
<td>11.6 (10.5,12.9)</td>
<td>411.1 (359,471)</td>
<td>45.8 (40,53)</td>
<td>445.6 (323,615)</td>
</tr>
<tr>
<td>Fold change</td>
<td>35</td>
<td>3.8</td>
<td>38</td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>
Qualitative assessment of vaccine response - Avidity

Typbar - TCV potentiates high-avidity antibody responses, that persist after a second dose of the vaccine.
Qualitative assessment of vaccine response – IgG Subclass

Typbar-TCV immune response included all sub-classes of IgG
Typbar-TCV conjugate vaccine

- Safe in all ages, including infants and children.
- Highly Immunogenic
  - High titre IgG response.
  - Immune response in children < 2 years.
- Persistent, Vi specific antibody response.
- High avidity anti-Vi IgG, including multiple IgG subclasses.
- Potentiates booster responses.
• Long-term follow-up underway for Phase III subjects.
  ✓ 3-year follow up and data analysis is ongoing.

• TCV-Measles interference study
  ✓ Enrollment complete: study ongoing

• Passive Surveillance: continuing

• Active Surveillance: Awaiting regulatory approval

• Human Challenge Study in collaboration with Oxford University: Regulatory approvals completed
TCV Measles Interference – Study design

A Phase IV, Randomized, factorial assigned, Open labelled, study to evaluate the non-interference in immune response of Typhoid Vi Capsular Polysaccharide - Tetanus Toxoid Conjugate Vaccine (Typbar-TCV™) administered to children at 9 months, to measles vaccine given concomitantly.

CTRI 2014/04/004532
Safety: Assessed at primary endpoints and long-term follow up.

Dose schedules: Single dose, single dose followed by booster at 6 months or 2 separated doses at 4 week interval.

Long term follow up: Subjects will be tracked for 2 years to test for persistence of anti-Vi titres in the 3 different TCV dose schedules.
Post-market passive surveillance

• Since the Product launch we have marketed close to one million doses of Typbar TCV

• PMS forms are being collected as part of the Passive Post Marketing Surveillance system

• No serious adverse reaction related to vaccine have been reported so far. Surveillance is ongoing.

• Active surveillance protocol submitted and pending regulatory approval. Surveillance expected to start in Q4 2015
Thank you!

“Team BHARAT Typbar-TCV”