Typhoid Conjugate Vaccine Development: The Last mile?

Sushant Sahastrabuddhe, MBBS, MPH, MBA
11th Typhoid conference
Hanoi, Vietnam
26th March 2019
What changed since Kampala 2017?

A lot....

In 2017,

- 2 TCVs licensed in India
- No TCV WHO Pqed
- WHO position paper 2008
- Gavi commitment, but pending WHO PQed TCV
- Unclear pathway for PQ
- No vaccine delivery projects
Policy and Financing (2019)

- **Policy:**
  - WHO position paper: 2008; revised in 2018
  - Recommended use of TCV

- **Vaccine supply:**
  - 3 licensed in India
  - Typbar-TCV prequalified by WHO

- **Financing:**
  - Gavi board has approved $85M for TCV and the call is open for eligible countries to apply
Delivery

Three ongoing campaigns

Navi Mumbai Municipal Corporation launches the world’s first public-sector typhoid conjugate vaccine campaign

Posted on September 17, 2018 by Dr. Kashmira Date, Medical Officer, Global Immunization Division, Center for Global Health, US Centers for Disease Control and Prevention

In Photos: A new vaccine to combat XDR typhoid in Pakistan

Posted on November 15, 2018 by Megan Carey, Bill & Melinda Gates Foundation

- Mumbai: 320,000 planned to be vaccinated in 2 phases
- Pakistan: over 100,000 kids vaccinated
- Zimbabwe: more than 300,000 planned to be vaccinated

Drug resistance and typhoid in Zimbabwe: Using TCVs for outbreak control

Posted on November 12, 2018 by Jessica Musonye, PATH
Effectiveness studies

• **TyVAC consortium** (Funded by BMGF):
  – 4 countries (Bangladesh, Nepal, Malawi, Burkina Faso)
  – Over 100,000 enrolled in the first 3 sites

• **THECA consortium** (Funded by EDCTP and BMGF):
  – 2 countries (Ghana and DRC)
  – Studies to initiate Q32019

These studies will collectively generate lot of data required by policymakers and will add to the existing knowledge gaps in TCV introduction
Lot of positives so far.....

- Global typhoid community aligned
- Major donors interested in typhoid prevention
- Policy and financing pieces are moving well
- Strong manufacturer with PQed vaccine
- Multiple delivery and effectiveness studies

However, to keep the momentum, supply security will be a challenge.....
Vaccine Demand and Supply

• As for any new vaccine introductions, the demand is not clear and depends on various uptake scenario in the endemic countries

• Gavi’s forecast:
  – Higher scenario: peaking at above 150 million doses in 2022, with a period of several years where demand could be well over 100 million doses per year, stabilizing later at levels above 70 million doses per year
  – Even with the lower scenario, demand is going to stabilize at >10M doses/year

• Multiple prequalified candidates will alleviate the supply insecurities and create healthy price competition
Typhoid conjugate vaccine pipeline

1994-2010

- Preclinical stage
  - NIH Vi-rEPA development - not commercialized
  - (Phase I-Phase III efficacy, Infant co-admin)

- Phase I
  - Biological E (B)
  - BioMed (licensed 2008)

- Phase II
  - PT Biofarma (A)
  - Bharat (licensed 2013)

- Phase III
  - SK Chemicals (A)

- National licensure
  - LIBP

- Phase 4 studies
  - Zydus (Licensed 2018)

(A) IVI technology transfer
(B) NVGH technology transfer

- Vi-CRM$_{197}$
- Vi-DT
- Vi-TT
- Vi-rEPA
- Under review

Slide courtesy: Dr Adwoa Bentsi-Enchill
Vi-rEPA clinical trials (First TCV developed)

- **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

- 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
Typbar-TCV

• First WHO Prequalified TCV (2018)
• Licensed in India plus 4 other countries
• Underwent human challenge study at Oxford University
• Being used in all delivery campaigns and effectiveness studies mentioned in the previous slides
• Only global public health market supplier of TCV for next 2 years
Vi-TT (ZydusCadila)

- Licensed in India (2018)
- Single dose 25ug from 6 months of age onwards
- Being marketed in the private market in India
- Plans to go for WHO PQ application in 2019
Vi-TT Pedatyph™ (Biomed)

- 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](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-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
• In summary,

  – Phase I and II in European adults \(\rightarrow\) at least as immunogenic as ViPS (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) (Bhutta et al. *Lancet Infect Dis* 2014)

  – Anti-Vi IgG titers after 1 dose 5 µg Vi \(\geq\) ViPS 25 µg (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).

  – **Antibody titers short-lived (~ 6 m); apparent lack of booster response.**

  – Technology transferred to Biological E, India and is currently in phase II/III clinical trial
Vi-DT: SK Bioscience

- Technology transfer completed in 2013 from IVI
- Preclinical studies completed in 2015
- Phase I clinical trial completed in the Philippines
- Phase II study ongoing in the Philippines
- Plans underway for phase III studies (Nepal and Philippines)
# Brief overview of the clinical trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study Design</th>
<th>Sample size</th>
<th>Test Vaccine /Comparator</th>
<th>Country</th>
<th>Status</th>
<th>Safety Database (test vaccine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Safety &amp; Immunogenicity</td>
<td>144 subjects (2-45 yrs)</td>
<td>Vi-DT, 25 µg/0.5 mL SD/ Typhim Vi®</td>
<td>Philippines</td>
<td>Completed</td>
<td>Approx. 72 subjects</td>
</tr>
<tr>
<td>II</td>
<td>Safety &amp; Immunogenicity</td>
<td>285 subjects (6-23 months)</td>
<td>Vi-DT, 25 µg/0.5 mL SD/ Fluquadri/ Placebo</td>
<td>Philippines</td>
<td>Ongoing, Interim report available in Nov 2018</td>
<td>Approx. 228 subjects</td>
</tr>
<tr>
<td>III</td>
<td>Immune Non-inferiority, L2L Consistency &amp; Safety</td>
<td>1800 subjects (6 mths-45 yrs)</td>
<td>Vi-DT,25 µg/0.5 mL MD/ Typbar TCV™</td>
<td>Nepal (4 sites)</td>
<td>Target start (July 2019)</td>
<td>Approx. 1350 subjects</td>
</tr>
<tr>
<td>III</td>
<td>Immune Equivalence &amp; Safety</td>
<td>1800 subjects (6 mths-45 yrs)</td>
<td>Vi-DT, 25 µg/0.5 mL SD/ MD</td>
<td>Philippines</td>
<td>Target start (Dec 2019)</td>
<td>Approx. 1500 subjects</td>
</tr>
</tbody>
</table>

**Total Safety Vi-DT database** | Approx. 3150
Vi-DT: Biofarma

- Technology transfer completed in 2013 from IVI
- Preclinical studies completed in 2015
- Phase I clinical trial completed in Jakarta, Indonesia
- Phase II study ongoing in Jakarta, Indonesia; interim report to be available end-March 2019
- Plans underway for phase III study (3 sites in Indonesia)
TCV Research Priorities (WHO)

• To generate data that will further support typhoid vaccination policy and immunization programs, particularly through research in the following areas:
  – Development of tools or methods to identify populations and individuals at risk of typhoid fever;
  – The risk of transmission from chronic carriers of S. Typhi and strategies to identify and treat carriers;
  – Correlate(s) of protection for typhoid vaccines;
  – Co-administration with other childhood vaccines (where not yet studied);
  – Safety and immunogenicity in special populations, including malnourished children, immunocompromised persons, and pregnant women;
  – Duration of protection after a single dose of TCV and the potential need for revaccination;
  – whether the tetanus toxoid carrier protein of the Vi-TT conjugate vaccine provides protection equivalent to a booster dose of tetanus vaccine; and
  – The impact of different TCV strategies including target age ranges for routine and catch-up vaccination as well as vaccination for outbreak control.
Acknowledgements

Manufacturers

- SK Chemicals
- PT Biofarma
- Incepta vaccines limited
- Bharat Biotech Ltd.
- Biomed
- Zydus Cadila
- Biological E
- Lanzhou Institute of Biological Products
- Finlay Institute
- Eubiologics

- Anita Zaidi
- Duncan Steele
- Megan Carey
- Lyou-Fu Ma
- Peter Dull
- Shauna Metschke
- Zoey Diaz
- Tina Lorenson
- Pat Brill Edwards
- Raysam Prasad

- Kate O’Brien
- Adwoa Bentsi-Enchill
- Joachim Hombach
- Thomas Cherian
- Carmen Rodriguez
- Olivier Lapujade
- Ivana Knezevic

- Denise Garrett

Regulatory authorities

- Korean MFDS
- Philippines NRA
- Indonesia BPOM
- Nepal DDA
- Nepal NHRC

- IVI Typhoid program team and support staff

- Kathy Neuzil
- Andy Pollard
- Anthony Marfin

- Hope Johnson
- Sjoerd Rijpkema
- Frank Gao
Acknowledgements

Jerome Kim
Julia Lynch
Phil Driver

IVI Clinical development and Regulatory team:
• Anh Wartel
• Jean-Louis Excler
• Tarun Saluja
• Arijit Sil
• Suchada Chinaworapong
• Jiwook Park
• Bo MI Kim

Project manager:
• Sue-Kyoung Jo

Project Administrators:
• Soyoon Chang
• Jae-in Lee

Epidemiology team:
• Florian Marks
• Se Eun Park
• Nimesh Poudyal
• Justin Im

Process Development team:
• Viliam Pavliak
• So Jun An

Biostatics and Data Management team:
• Yun Chon
• Deok Run Kim
• Ju Yeon Park
• Saemina Kang

Clinical Immunology team:
• Manki Song
• Jae Seung Yang
• Yun-Ji Jang
• Eun Young Lee

Policy and Health Economics team:
• Vittal Mogasale
• Dayoung Song
• Enusa Ramani
• Jung Seok Lee

Quality Assurance:
• Tobin Guarnacci
• Minseon Lee
• Yong Min Kim
# SK Vi-DT Phase I Study

**Objectives**

**Primary**
- To evaluate the safety of 25 µg of Vi-DT typhoid conjugate vaccine administered at 0 and 4 weeks

**Secondary**
- To assess the immunogenicity of 25 µg of Vi-DT typhoid conjugate vaccine administered at 0 and 4 weeks
- To compare the safety and immunogenicity of Vi-DT and Vi-Polysaccharide typhoid vaccines

## Purpose
Evaluate the safety of 25 µg of Vi-DT typhoid conjugate vaccine
Assess the immunogenicity of 25 µg of Vi-DT typhoid conjugate vaccine
Compare the safety and immunogenicity of Vi-DT and Vi-Polysaccharide typhoid vaccines

## Country
Philippines

## Study Design
Randomized, observer-blinded, age de-escalating, safety and immunogenicity study

## Target Age
Adults 18 to 45 years of age; adolescents 6 to 17 years of age; children 2 to 5 years of age
Total: 144 participants

## Comparison
**Test Vaccine:** Vi-DT (25 µg of Diphtheria Toxin-conjugated Vi polysaccharide) typhoid vaccine  
**Comparator Vaccine:** Typhim Vi® (25 µg of Vi-polysaccharide) typhoid vaccine

## Schedule

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>N</th>
<th>Study arm</th>
<th>1st Vaccination (Week 0)</th>
<th>2nd Vaccination (Week 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-45</td>
<td>24</td>
<td>Test</td>
<td>Vi-DT</td>
<td>Vi-DT</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Comparator</td>
<td>Typhim Vi®</td>
<td>VAXIGRIP®</td>
</tr>
<tr>
<td>6-17</td>
<td>24</td>
<td>Test</td>
<td>Vi-DT</td>
<td>Vi-DT</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Comparator</td>
<td>Typhim Vi®</td>
<td>VAXIGRIP®</td>
</tr>
<tr>
<td>2-5</td>
<td>24</td>
<td>Test</td>
<td>Vi-DT</td>
<td>Vi-DT</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Comparator</td>
<td>Typhim Vi®</td>
<td>VAXIGRIP®</td>
</tr>
</tbody>
</table>
Summary: Results

Vi-DT is safe, generally well tolerated and immunogenic

Phase I (in progress)

Safety

- No subject was withdrawn from the study due to AE
- AEs balanced between groups, mild and moderate - No SAE
- Majority of solicited AE
  - ✓ in adults are pain, tenderness and headache.
  - ✓ In adolescent are pain and tenderness
  - ✓ In young children are pain and fever

Immunogenicity

- 100% seroconverted after the first dose
- Second dose does not increase GMT
- Vi-DT GMT are 4-fold higher than Typhim Vi
SK Vi-DT Phase II Study

Study Title:
A Phase 2, Randomized, Dose-scheduling, Observer-Blinded Study to Assess the Safety, Reactogenicity and Immunogenicity of Vi-DT Conjugate Vaccine in 6-23-Month old Healthy Infants and Toddlers

Number of participants: 285

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Vaccinees</th>
<th>Vaccination Schedule (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>114</td>
<td>0: VI-DT** 25 µg 0.5 mL, FluQuad™ * 0.25 mL, VI-DT 25 µg 0.5 mL</td>
</tr>
<tr>
<td>B****</td>
<td>114</td>
<td>0: VI-DT** 25 µg 0.5 mL, VI-DT 25 µg 0.5 mL, No VI-DT boost</td>
</tr>
<tr>
<td>C</td>
<td>57</td>
<td>0: Placebo**, FluQuad™ * 0.25 mL, N/A</td>
</tr>
</tbody>
</table>

Primary Objectives:
- Assess and describe the safety and reactogenicity of Vi-DT
- Assess and compare anti-Vi seroconversion rate 4 weeks post dose one [of combined one and two-dose regimens] of Vi-DT to comparator group
Phase III considerations (continued)

- We have developed a two-pronged strategy for conduct of the phase III trial:
  1. We will conduct the non-inferiority study with Typbar-TCV along with the lot to lot consistency in Nepal (sample size ~1800)
  2. We will conduct another phase III study in the Philippines for additional safety data generation as well as to immune equivalence of single dose formulation (used in phase I and II) against multiple dose formulation (To be used in the phase III)