INTERNATIONAL VACCINE INSTITUTE

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

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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

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

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:
  - Pedatyph ®
  - Typbar-TCV®

Vi-rEPA: US NIH

- 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

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

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

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MAJOR ARTICLE

Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study

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Background. Enteric fever caused by *Salmonella* Typhi remains a major public health problem in developing countries. Typbar-TCV is a single-dose typhoid Vi polysaccharide–tetanus toxoid conjugate vaccine for persons ≥6 months of age.

Methods. Six hundred fifty-four healthy subjects aged 2–45 years enrolled in a double-blind, randomized controlled trial (RCT) received a single dose of Typbar-TCV or comparator "Vi polysaccharide" (Typbar), and 327 healthy subjects aged 6–23 months received a single dose of Typbar-TCV in an open-label trial (OLT); both received single- or multidose presentations from different lots. After 2 years, subsets in each group received a booster dose. The primary objective included analysis of geometric mean titer (GMTs) and 4-fold rise of anti-Vi serum immunoglobulin G (IgG) enzyme-linked immunosorbent assay titers over baseline (seroconversion [SCN]) 42 days after immunization.

Results. Typbar-TCV recipients in the RCT attained higher anti-Vi IgG GMTs 42 days after immunization (SCN, 97%; GMT, 1293 [95% confidence interval {CI}, 1153–1449]) than recipients of Typbar (SCN, 93%; GMT, 411 [95% CI, 359–471]) ($P < .001$). Typbar-TCV was highly immunogenic in the OLT (SCN, 98%; GMT, 1937 [95% CI, 1785–2103]). Two years after vaccination, anti-Vi titers remained higher in Typbar-TCV subjects (GMT, 82 [95% CI, 73–92]); and exhibited higher avidity (geometric mean avidity index [GMAI], 60%) than in Typbar recipients (GMT, 46 [95% CI, 40–53]; GMAI 46%) in the RCT ($P < .001$). OLT Typbar-TCV recipients achieved GMT of 48 (95% CI, 42–55) and GMAI of 57%. Typbar-TCV induced multiple IgG subclasses and strong booster responses in all ages. No serious vaccine-attributable adverse events were observed.

Conclusions. Single-dose Typbar-TCV is well tolerated and induces robust and long-lasting serum anti-Vi IgG across age groups.

Clinical Trials Registration. CTRI/2011/08/001957, CTRI/2014/01/004341.

Keywords. typhoid; conjugate vaccine; booster; persistence; avidity.

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Enteric fever caused by *Salmonella enterica* serovar Typhi and *Salmonella enterica* serovar Paratyphi A and B remains a public health problem among populations lacking treated drinking water and improved sanitation in many developing countries [1–3]. In most

Mohan VK et al., Clin Infect Dis. 2015; 61(3):393-402.

Vi-TT (BBIL)

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 Typbar-TCV Compared With Day 0

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

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.

- 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

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)

Vi-TT (Biomed)

Pedatyph ™ 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

Vi-TT (Biomed)

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RESEARCH PAPER

Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study

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- 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

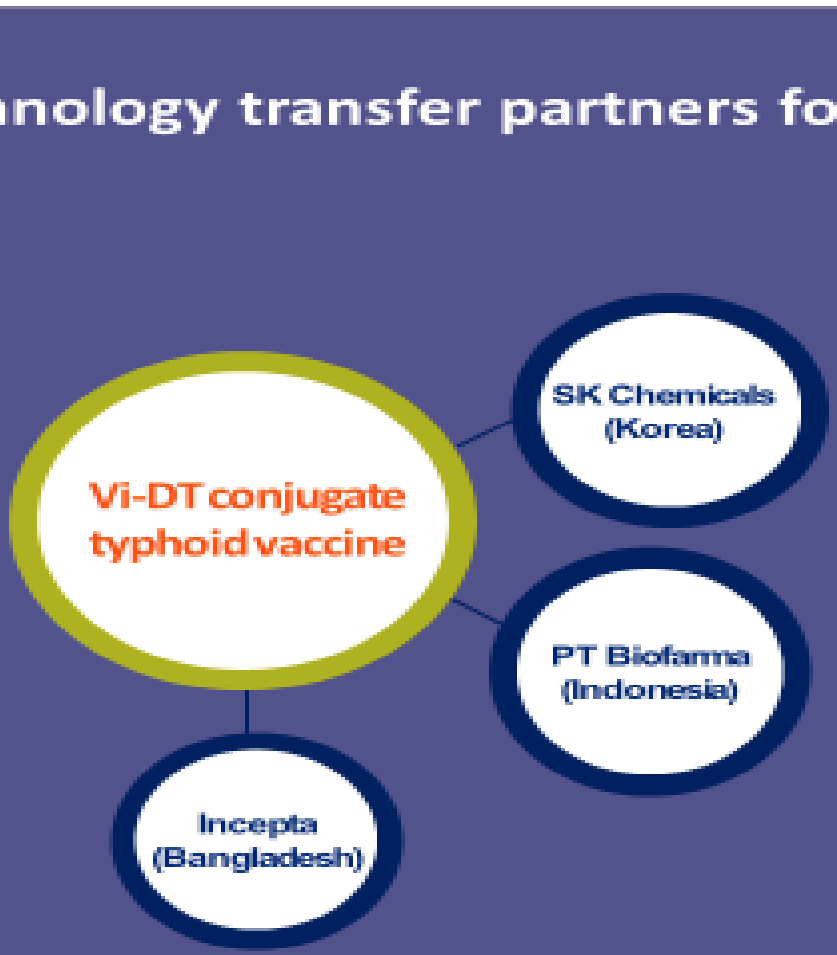
- Safety, Reactogenicity and Immunogenicity of Vi-CRM197 Vaccine Against S. Typhi in Adults, Children, Older Infants (9 to 12 months) and Infants (6 weeks)
- 320 participants, studies completed in India, Philippines, and Pakistan

Vi-CRM$_{197}$ (GVGH)

- In summary,
  - Phase I and II in European adults → 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 >= 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 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

Vi-DT: Additional manufacturers

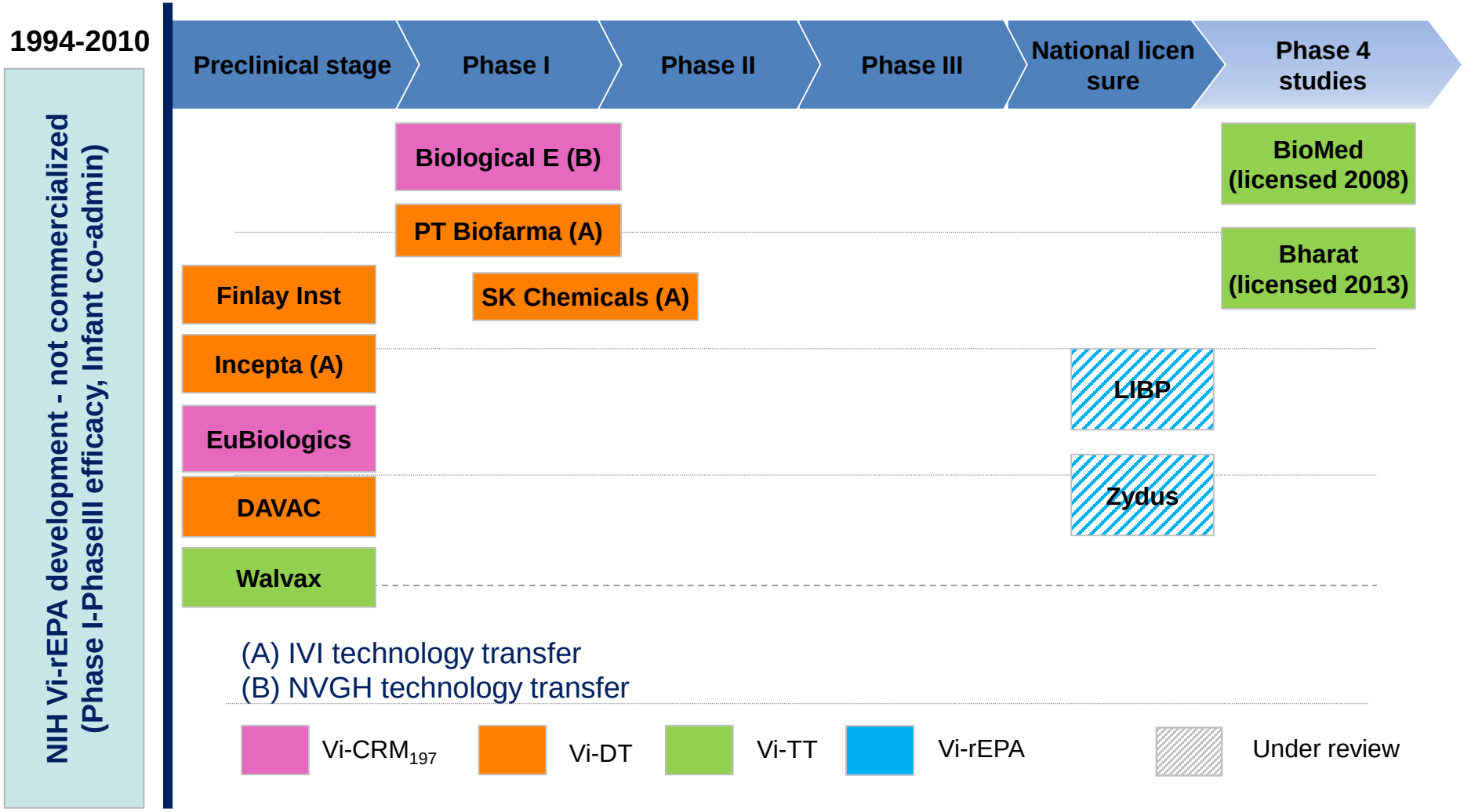
Biofarma:

- 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



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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- Lanzhou Institute of Biological Products
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- Incepta Vaccines Ltd
- Finlay Institute
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