

Updates on Typhoid Conjugate vaccine Development: IVI

Sushant Sahastrabudde

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Outline of the presentation

- Need for a typhoid conjugate vaccine
- IVI's work in Typhoid Fever (DOMI, VIVA, TSAP)
- Brief history of IVI's typhoid conjugate vaccine development program
- Updates on the Vi-DT vaccine development status
- Timelines
- Future Development plans

Issues with currently available typhoid vaccines

Issues with current oral typhoid vaccine (Ty21a)

- Multiple doses needed
- Strict cold chain requirement
- Not available for children < 5 years of age

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)

Newer Typhoid Vaccines in Development

Vaccines developed through genetic mutations

- CVD 908: mutation in *aroC/aroD*
- CVD 908-htrA: further mutation in *htrA*
- CVD 909: Replaced P_{tviA} with P_{tac} of CVD 908-htrA
- Ty800: mutation in *phoP/phoQ*
- X3927: mutation in *cya* and *crp*
- MO1ZH09: mutation in *aroC* and *ssaV*

Vaccines developed using 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[®]
- Typhoid vaccine:
 - Pedatyph[®]

IVI's work in Typhoid fever

- **DOM I:**

Prospective population based disease burden studies conducted in 5 different countries in Asia

- **VIVA Initiative:**

1. To ensure the licensure and WHO pre-qualification of a Vi conjugate vaccine
2. To ensure a cost-competitive supply of Vi polysaccharide vaccine
3. To accelerate the adoption of Vi polysaccharide vaccine in high-risk areas
4. To prepare an investment case and developing an advocacy strategy

- **TSAP:**

Typhoid disease burden in Africa through establishment of surveillance sites

Programmatic Introduction Strategies

	Gaps	VIVA's attempt to bridge the gaps
Vaccine	<p>Typhoid vaccines not WHO prequalified</p> <p>Licensed only for age 2 years and above</p>	<p>Facilitate prequalification of existing and future vaccines</p> <p>Development of Vi-DT conjugate vaccine</p>
Introduction strategy	<p>Current typhoid vaccines not suitable for EPI schedule</p> <p>New implementation platform required in many countries</p>	<p>Pilot school-based typhoid vaccine introduction projects in high endemic countries</p>
Financing	<p>Typhoid vaccine is not GAVI supported</p>	<p>Cross-subsidization: novel financing mechanism</p>
Policy and Advocacy	<p>Only endemic provinces in China, Vietnam, and Delhi State (India) have introduced the vaccine as a routine program</p>	<p>Medical Officer at WHO HQ to facilitate communication with Regional Offices and countries</p> <p>Vaccine investment case development</p>

Typhoid conjugate vaccine: Vi-DT

- With the initial know-how from US NIH, IVI developed the technology to adopt for developing country manufacturers:
 - The step of phenol extraction was removed
 - Carrier protein was changed to DT as DT is easy/ cheap to produce, has regulatory precedence, and is manufactured by many developing country manufacturers
 - The yield of Vi polysaccharide had been increased 7-fold through process optimization.
 - The conjugation process has been optimized to attain at least 40% recovery for the final product.

Typhoid conjugate vaccine: Vi-DT

- Shantha Biotechnics in India was identified as manufacturing partner after a due diligence process
- The technology to manufacture Vi-DT was transferred to Shantha
- Shantha has completed the toxicology study and have produced clinical trial lots
- The regulatory dossier has been submitted to DCGI in December and the approval is expected in May/ June

Functional Assay Development

- Working in close collaboration with University of Vermont, IVI is developing the Opsanophagocytic assay for S. Typhi
- This will not be required either for local licensure in India or for WHO PQ; but will help in better quantifying the results of the data coming out from the clinical studies
- In the initial work conducted at IVI, we have seen some serum bactericidal activity and this work will be validated soon

Target Product Profile

	Characteristics
Age Group	All age groups; targeting 9 months and above for first licensure
Route	Intramuscular
Dose	25 or 12.5 or 5 mcg; to be explored and finalized in Phase II studies
Presentation	Vials (PFS to be explored based on business needs)
No of doses (Schedule)	Age group 9 months to 2 years: 2 doses (9 months + booster at 15- 18 months) Age group > 2 years: 1 dose Age 6 weeks to 9 months: 2 or 3 doses (to be explored)
Co-administration	Co-administration possible with concomitantly administered vaccines for age group
Target Countries	India; WHO PQ; Public funded markets in Asia, Africa and Latin America
Shelf life	36 months at 2-8 degrees Celsius

Vi-DT Clinical Development Plan

Phase	Country	Subjects	Objectives and Design	Comments	Vi DT database
I	India	360	Safety; Non inferiority of immunogenicity vs a polysaccharide vaccine Age groups; 2-18 years & 18 + years	Three arm parallel, randomized , observer blinded	120
II	India	240	Safety and Immunogenicity; Dose exploration (25 vs 12.5 vs 5 mcg); two doses administered at 9-10 and 15-18 months;	Three arm parallel, randomized, observer/ double blind	180
III	India	500	Safety and Immunogenicity; Functional Assay; Co-administration with MMR; DTP; Hib; Age – 9- 18 months; immune non interference	Two arm, randomized, observer/ double blinded	250
IV	India	2000	Safety follow up; long term immunogenicity follow up (12, 18, 24, 30, 36), 6 months safety.	Multi-centric	2000

Timeline

	Start	End
ECV01 (Phase I)	Jun 2013	Feb 2014
ECV02 (Phase II)	Aug 2014	Oct 2015
ECV03 (Phase III)	Apr 2016	Jul 2017
<i>ECV04 (Phase III)</i>		
India Licensure		Jan 2018
WHO PQ		Mar 2019

- IVI- BioFarma partnership:
 - MoU has been signed and the technology to manufacture Vi-DT will be transferred in 2013

- IVI-SK chemicals partnership:
 - MoU has been signed and the technology to manufacture Vi-DT will be transferred in 2013

Typhi-Paratyphi A bivalent vaccine

- IVI's work in Paratyphoid
- Prospective population based disease burden data from DOMI Typhoid Program
 - Paratyphoid fever is becoming a significant problem in Asia
 - More paratyphoid than typhoid fever detected in Guangxi province in recent years

Ochiai et al. Emerg Infect Dis. 2005

Many reports in Asia since have confirmed the high burden of SPA

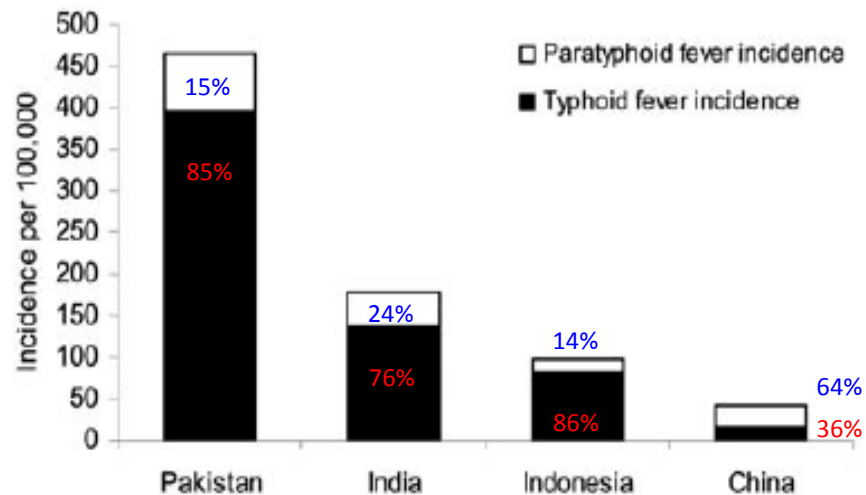


Figure. Incidence of *Salmonella enterica* serovar Typhi and *S. Paratyphi A* in 4 Asian countries.

Typhi-Paratyphi A bivalent vaccine

- IVI's work in Paratyphoid
- PARACHINA Program:
 - To generate the multi-disciplinary evidence needed to inform policymakers whether introduction of vaccines against paratyphoid is warranted and can be accomplished in a feasible and sustainable fashion in Guangxi province, China
 - Explored the burden of paratyphoid fever through a population based study in Hechi, Guangxi Province
 - Incidence of blood culture confirmed paratyphoid fever was 10/100,000 per year in the 3-year study period

Paratyphoid A carrier survey:

- We followed up 353 historical SPA cases by collecting stool and blood samples
- The prevalence of SPA carriage status among historical SPA cases was 2%.

Typhi-Paratyphi A bivalent vaccine

- IVI is developing a bivalent S. Typhi- S. Paratyphi A conjugate vaccine
- Monovalent Vi-DT process development is completed
- Monovalent OSP-DT process development is underway
- Optimization work is being done to prepare the final formulation of the bivalent vaccine

o Thank you!

