



INTERNATIONAL
VACCINE INSTITUTE

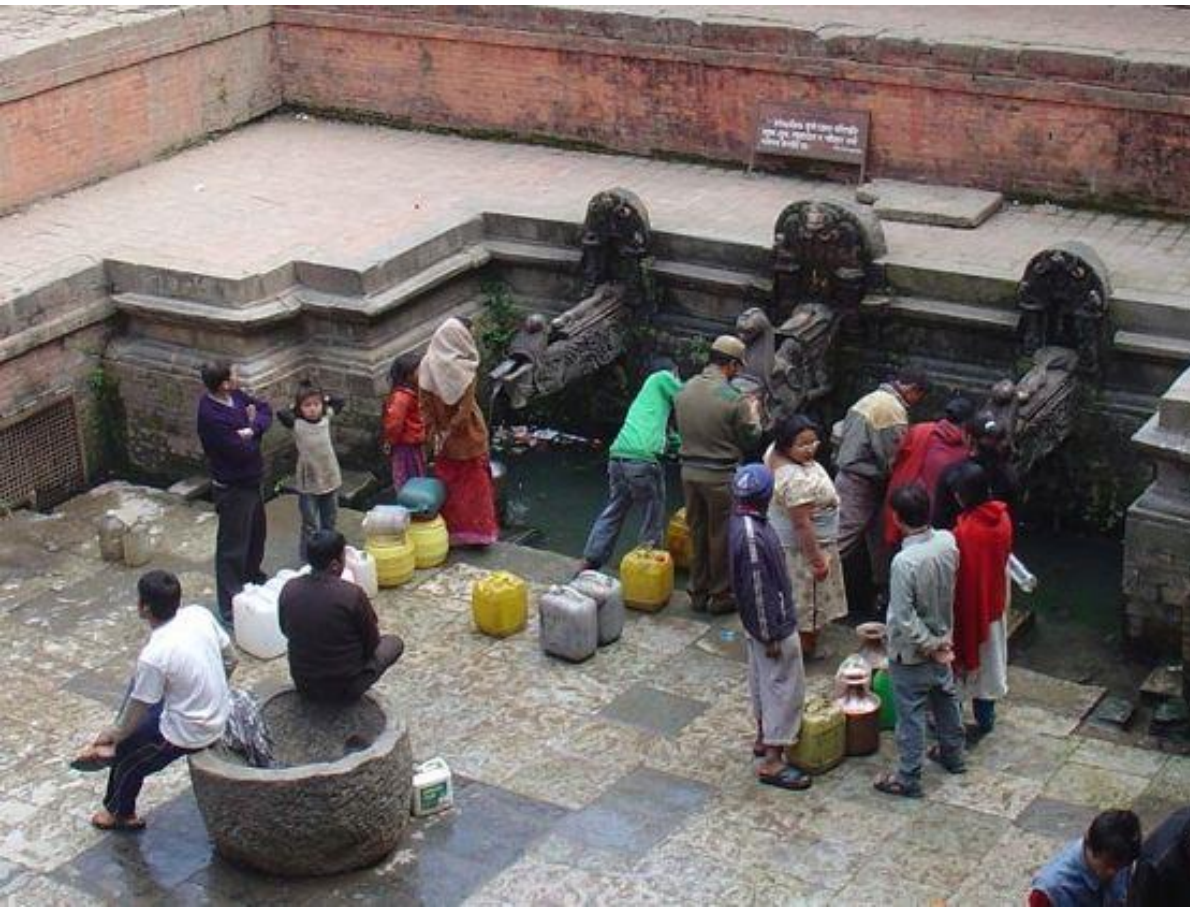
The current status of vaccine development for control of *Salmonella* Paratyphi A

Rodney Carbis (Head Vaccine Development, IVI)
9th International Conference on Typhoid and Invasive NTS Disease
Bali Indonesia 30 April – 5 May, 2015.

Enteric fever is still a significant health problem

Caused by *Salmonella enterica* serovars Typhi and Paratyphi.

Symptoms clinically similar.



S. Typhi was believed to be the major cause of enteric fever.

Asian country reports indicate that *S. Paratyphi*, mainly *S. Paratyphi A*, is increasing and in some communities is the predominant cause of enteric fever.



Vaccine development

Increase in the interest and use of typhoid vaccines in typhoid endemic countries.

Vaccine developers working on new generation typhoid vaccines particularly **Vi based conjugate vaccines.**



Paratyphoid vaccine development is, however, lagging behind.



Vi conjugate vaccines

| No. | Manufacturer | Location | Tech Transfer Agreement | Product details | Clinical Dev't Status |
|-----|---------------------------------|------------|-------------------------|-----------------|--|
| 1 | Bharat Biotech Int. Ltd. (BBIL) | India | Own R&D | Vi-TT | NRA Licensure in India |
| 2 | Shantha Biotechnics Ltd. (SBIL) | India | IVI | Vi-DT | Development stopped |
| 3 | Bio-Med Pvt. Ltd | India | Own R&D | Vi-TT | NRA Licensure in India |
| 4 | PT BioFarma | Indonesia | IVI | Vi-DT | Phase I clinical trial to start in 2Q 2015 |
| 5 | Finlay Institute | Cuba | Unknown | Vi-DT | Clinical development |
| 6 | Lanzhou Institute (CNBG) | China | US NIH | Vi-rEPA | NRA Licensure application submitted |
| 7 | SK Chemicals | S. Korea | IVI | Vi-DT | Phase I clinical trial will start in 4Q 2015 |
| 8 | Incepta | Bangladesh | IVI | Vi-DT | Preclinical studies to start |
| 9 | Biological E | India | NVGH | Vi-CRM | Phase I clinical trial planned |
| 10 | EuBiologics | S Korea | Own R&D | Vi-CRM | Pre-clinical |
| 11 | DAVAC | Vietnam | Own R&D | Vi-DT | Pre-clinical |
| 12 | Walvax | China | Own R&D | Vi-TT | Pre-clinical |

Paratyphoid vaccines

- No licensed vaccines against *Salmonella Paratyphi A*

In the early 1900s a heat inactivated whole cell vaccine containing *S. Typhi*, *S. Paratyphi A* and *S. Paratyphi B* (TAB vaccine). The vaccine was delivered parenterally and although moderately effective against Typhoid (51 – 88%) it was highly reactogenic (up to 30% of vaccinees with fever).

- Reactogenicity likely due to Lipopolysaccharide (LPS).
- O Specific polysaccharide (OSP) an integral part of the LPS is the protective antigen.



Live attenuated Paratyphoid vaccines

$\Delta phoPQ$ mutant *S. Paratyphi A* mutants have been tested for immunogenicity and reactogenicity, one strain (MGN10028) was well tolerated in rabbit model and could be considered for clinical evaluation.

CVD1902 - ATCC9150 (with *guaBA* and *clpX* deletions) in phase I clinical development



Subunit Paratyphoid vaccines

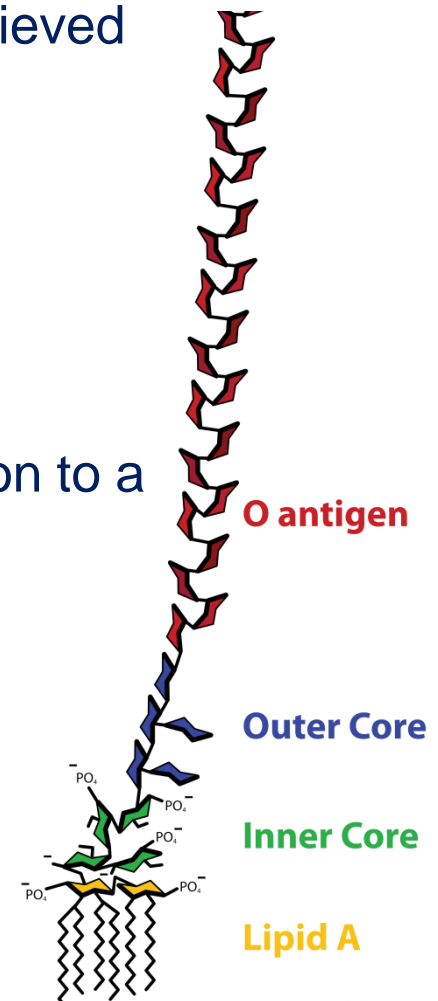
Subunit vaccine development has focused on the OSP

A critical level of anti-Paratyphi A OSP serum IgG is believed to be required to confer protection.

If vaccine is to be delivered parenterally

Need to reduce reactogenicity by removal of Lipid A

OSP alone is poorly immunogenic and requires conjugation to a carrier protein to induce an adequate (T-cell dependent) response.



Paratyphoid conjugate vaccines

NIH have led the way in *S. Paratyphoid A* conjugate development.

OSP-TT conjugates with and without ADH spacer molecules tested in phase I and II clinical trials in Vietnam.

Vaccine was immunogenic with no significant side effects.

Technology transfer of this vaccine to Lanzhou and Chengdu Institutes of Biological Products.

Changchun Institute of Biological Products is developing a similar product.

The Lanzhou product has been tested in phase I and II clinical trials



Other Paratyphoid A conjugates in pre-clinical development

Novartis Vaccine Institute for Global Health
CRM197 as the carrier protein

International Vaccine Institute
Tetanus Toxoid as the carrier protein

Walvax Biotechnology Co. Ltd.
Tetanus Toxoid as carrier protein

Bharat Biotech:
Plans for an OSP-conjugate vaccine



Salmonella Paratyphi A

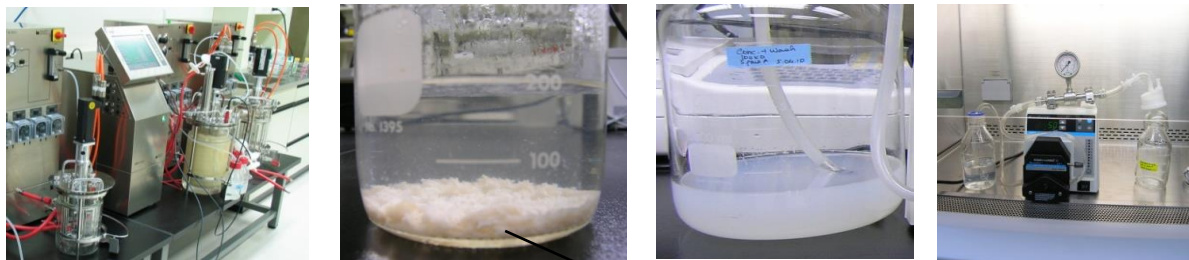
OSP-TT conjugate

Optimized bacterial growth in a fermentor

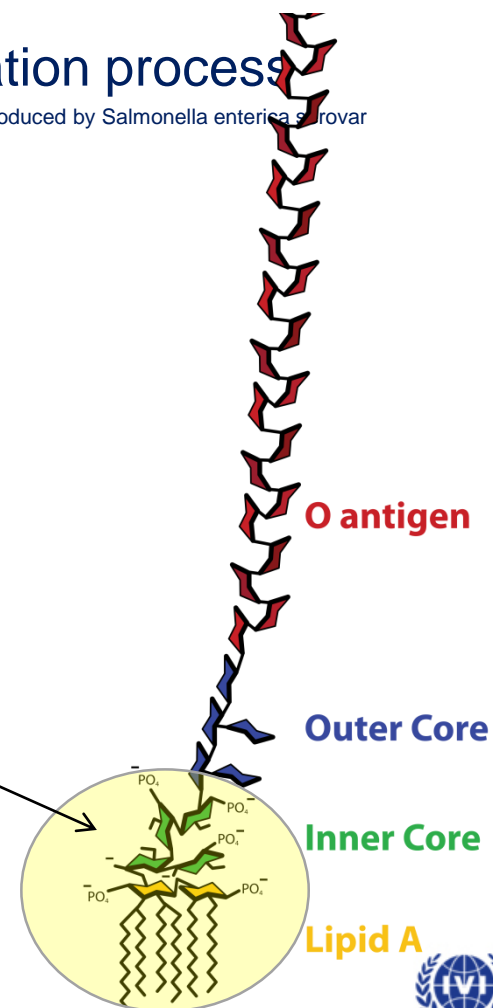
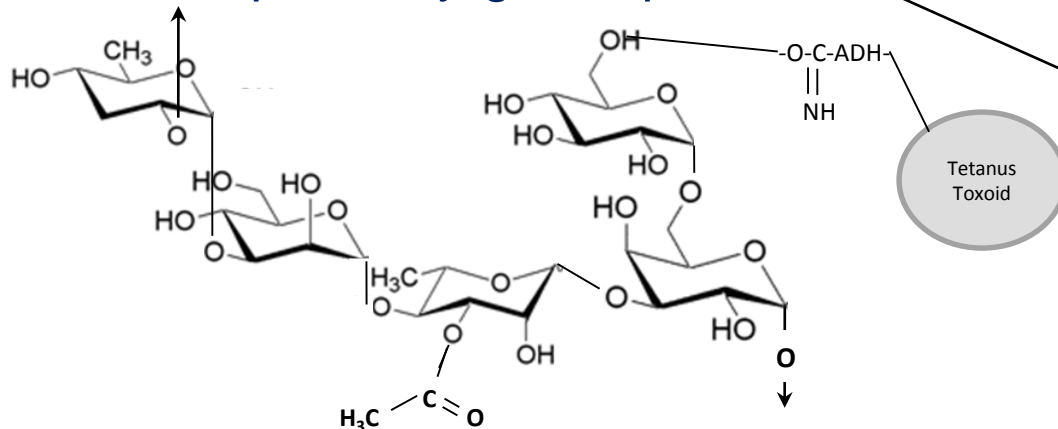
Developed a novel O-specific polysaccharide purification process

Kothari S, Kim JA, Kothari N, Jones C, Choe WS, Carbis R. Purification of O-specific polysaccharide from lipopolysaccharide produced by *Salmonella enterica* serovar Paratyphi A.

Vaccine 2014;32:2457-62



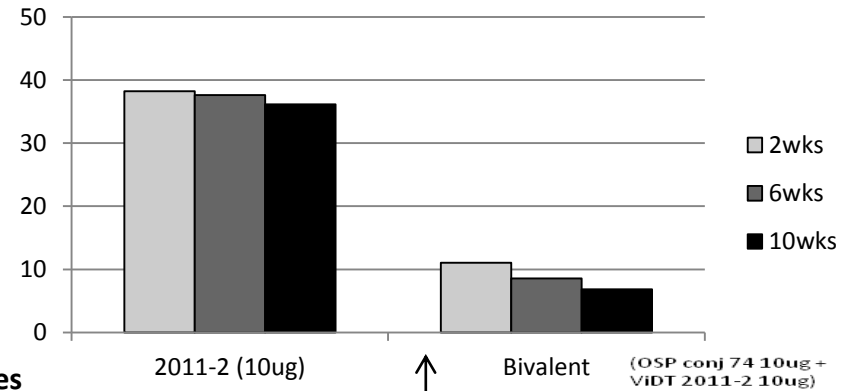
Developed conjugation process



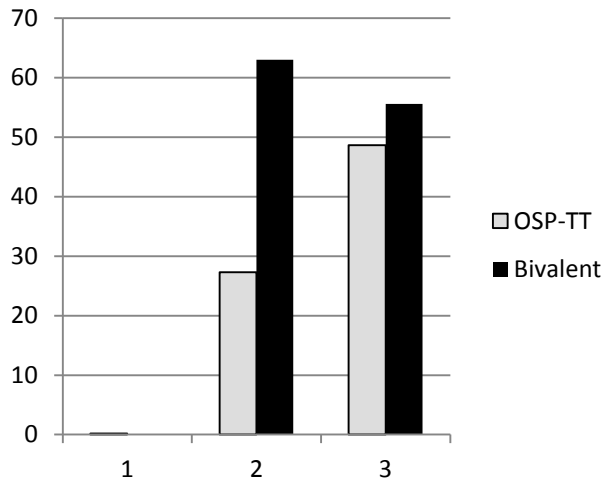
Vi-DT / OSP-TT conjugate

Formulated bivalent vaccine
Tested immunogenicity in mice

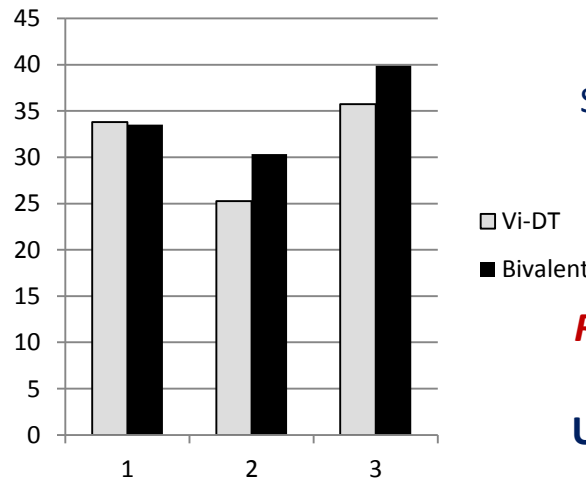
Inhibition of Anti Vi response in bivalent
Vi-DT / OSP-DT



Anti-OSP responses



Anti-Vi responses



Vi-DT / OSP-DT combination:
Significant immune response interference

Vi-DT / OSP-TT combination:
No interference

READY FOR TECHNOLOGY TRANSFER?

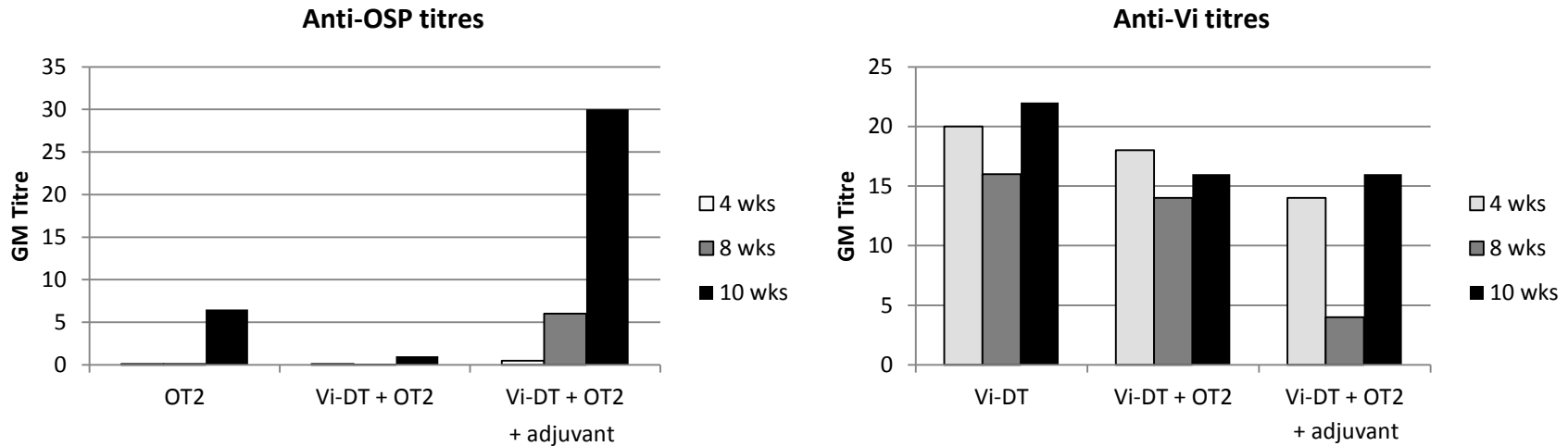
Unable to produce OSP-TT conjugate
with the same immunogenicity.

OSP-TT conjugate 165 was reproducibly immunogenic



Vi-DT / OSP-TT conjugate

Formulated bivalent vaccine with adjuvant



Adjuvant overcomes inhibition of antibody responses caused by OSP conjugates.

This could also be important with other OSP conjugates?
Such as with non-typhoidal salmonella (NTS) vaccine



Thank you

