



INTERNATIONAL  
VACCINE INSTITUTE

# Future typhoid conjugate vaccines



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ASTMH - New Orleans  
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# Moral obligation

Every person has the right to receive high quality, safe and efficacious vaccines to protect them from infectious diseases.

Typhoid vaccine is no exception

A significant disease burden exists in impoverished communities



## Limited funding

Funding for vaccination is limited so in order to get the broadest coverage in developing countries vaccines must be affordable



# How does IVI address affordability and supply

## Process development:

- High yielding antigen production
- High recovery purification process
- Scalable process compatible with cGMP production

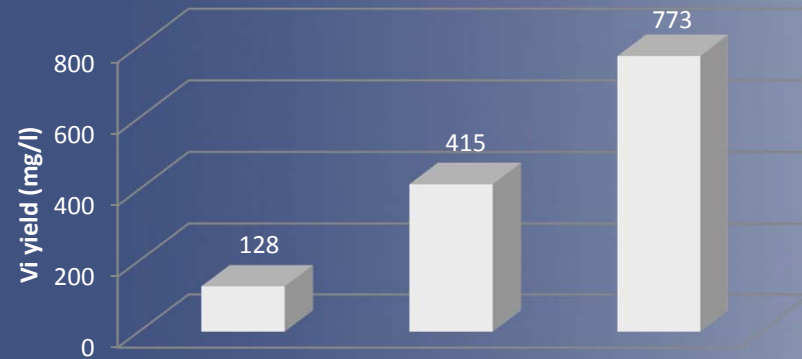


## Technology Transfer:

- High standards for quality, strict adherence to cGMP
- Manufacturers committed to low cost production and low margin sales
  - Developing Country Vaccine Manufacturers
- Manufacturer with capacity to WHO prequalify



# Production of Vi



1. Increased cell density by Fed batch fermentation
2. Increased Vi production by controlling glucose concentration
  - High glucose inhibited Vi production
  - High pH and high salt concentrations also inhibitory

# Purification

## Downstream processing (purification of Vi)

Removal of impurities

Maximize recovery of Vi polysaccharide



Clarification



Cells

Crude Vi



Crude Vi concentrate



Cetavlon precipitated Vi



Ethanol precipitated Vi



Vi dissolved in water



Purified bulk Vi

Seed bank  
Local Indian Isolate

Fermentation  
Inactivation

Clarification of Vi

Concentration  
Diafiltration

Cetavlon precipitation

Dissolve in 60% ethanol

Precipitate and wash  
with 75% ethanol

Dissolve in water

$(\text{NH}_4)_2\text{SO}_4$   
Precipitate impurities

Concentration / Diafiltration

Sterile filtration

**40% recovery - approximately 1,000,000 doses per 100 L fermentation**

# Conjugate Vaccine

## Vi polysaccharide only vaccines

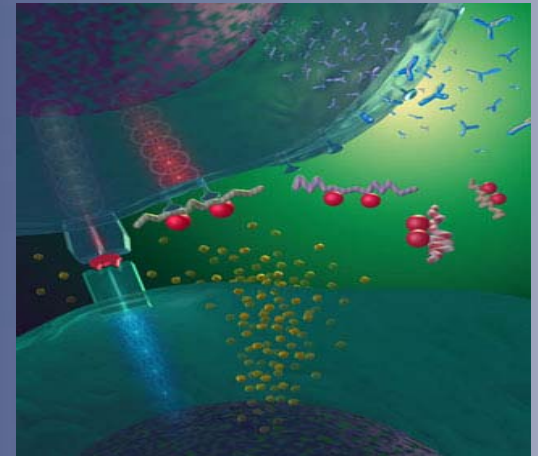
- Poor anti-Vi antibody responses in older children and adults
- **No response in infants (< 2 years of age)**
- No memory - no boosting
- Relatively short lived immunity

## Vi conjugate vaccine

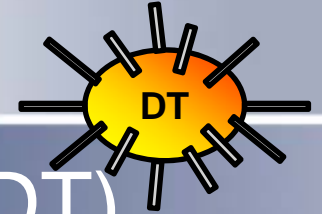
(polysaccharide bound to protein carrier)

Change the nature of the response to recruit T helper cells

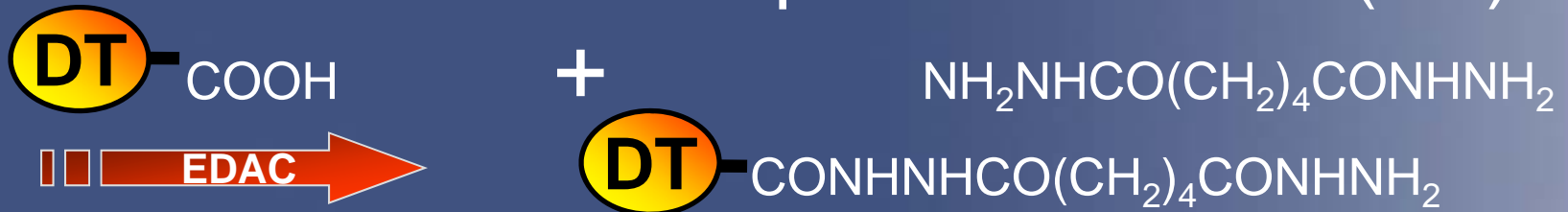
- **Higher antibody responses in all age groups including a response in infants**
- Induction of memory and boosting on revaccination
- Duration of immunity much longer



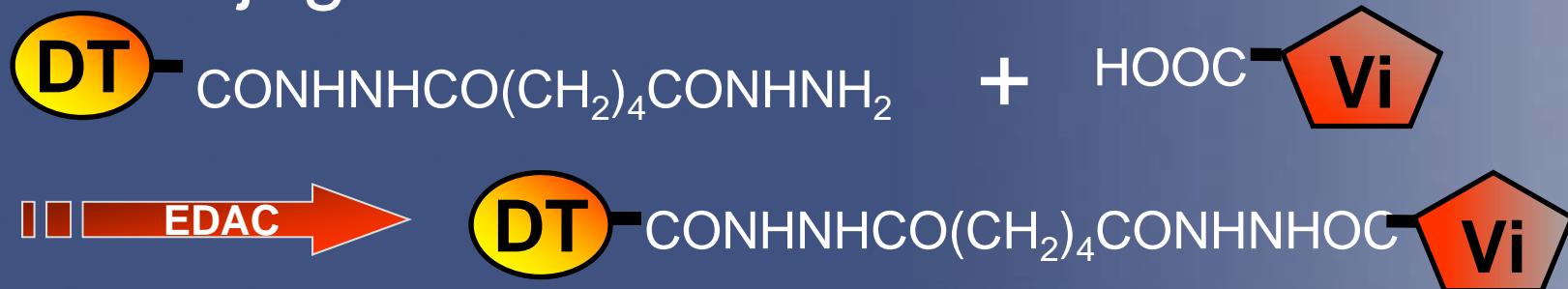
# Conjugation Chemistry



## 1. Derivatization of Diphtheria Toxoid (DT)



## 2. Conjugation



80% recovery of Vi – 800,000 doses per 100 L fermentation



# Technology Transfer

Initial training at IVI  
Follow up at manufacturer

Technology transferred to:

Shantha Biotechnics - India

SK chemicals - Korea

BioFarma - Indonesia

Incepta - Bangladesh

**Ensuring a reliable supply of vaccine**



60,000 dose pilot lot  
of Vi-DT



# Target population

- **The vaccine should be able to be administered during routine and mass immunization to various age groups including adults, children, and infants aged 9 months and above**
- **Delivery during the routine measles EPI will reduce the programmatic costs involved in vaccinating.**
- **Clinical trials with our three manufacturing partners will begin next year**
  - **Age descending to demonstrate safety and immunogenicity**
  - **In the target population will need to demonstrate vaccine can be safely co-administered with concomitantly scheduled, licensed vaccines**
  - **Does not result in antigen interference**

## Future vaccines being developed at IVI

There is limited funding for introduction of new vaccines particularly in developing countries so adding value to the typhoid conjugate vaccine may help to prioritize its introduction.

Enteric fever caused by *Salmonella* Paratyphi A (clinically indistinguishable from typhoid fever) ranges from 11 – 35% in some areas and is increasing where typhoid vaccination is active.

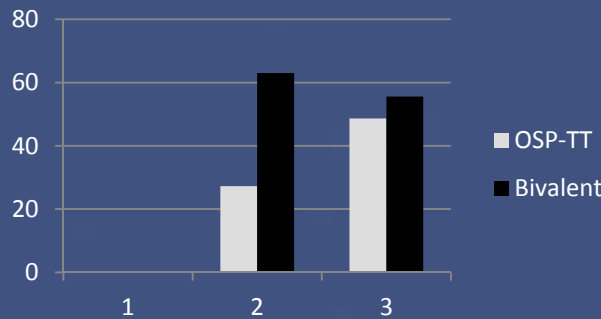
Using PspA (common pneumococcal surface antigen) as a carrier protein we may be able to have a typhoid vaccine that has the potential to also provide broad protection against *S. pneumoniae*.

Formulate Vi-DT conjugate with existing pediatric vaccines and deliver in EPI programs in typhoid endemic communities.

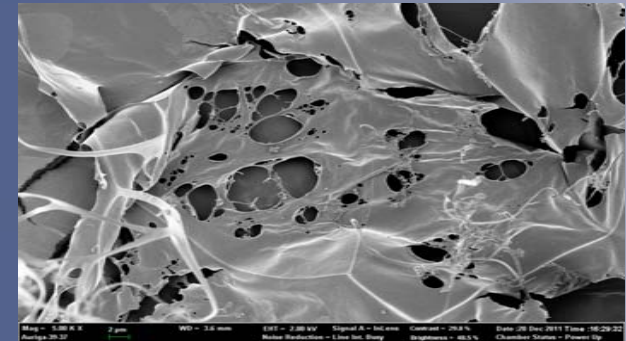
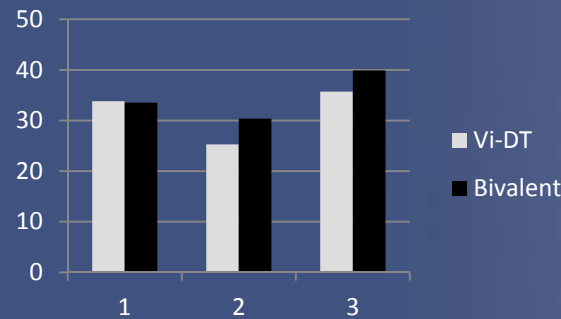
Benefits - no storage costs or additional burden on the cold chain  
- no delivery cost as administered with existing vaccine

# Bivalent Typhoid/Paratyphoid A conjugate vaccine

Anti-OSP responses



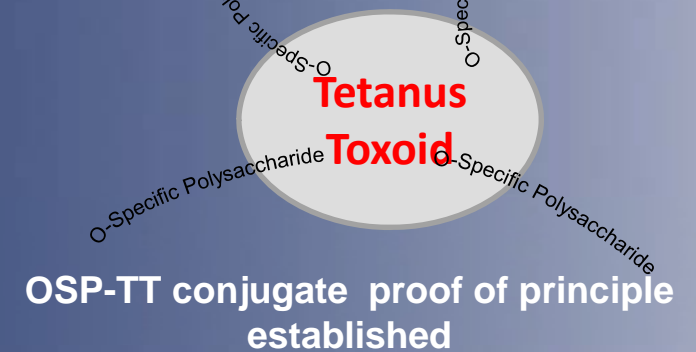
Anti-Vi responses



**Salmonella Typhi**  
Vi-DT conjugate developed and technology transferred

**Bivalent** proof of principle established

**Salmonella Paratyphi A**  
OSP purification process development completed



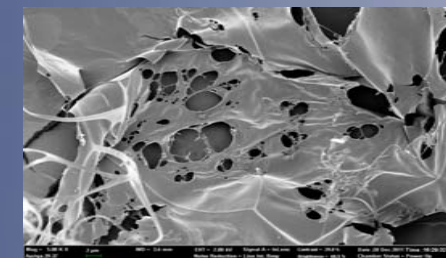
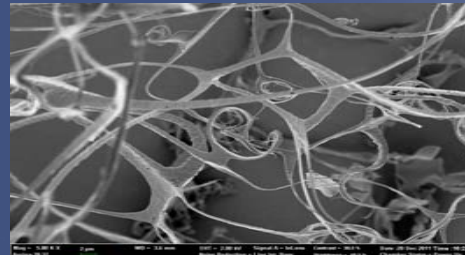
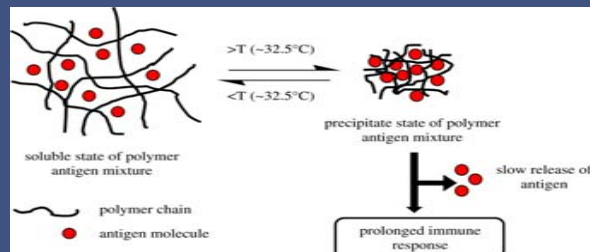
# Vi as an antigen presentation vehicle

During development of Vi-DT we observed that a single dose:  
Increased the anti-DT response for up to 12 weeks  
DT alone - poorly immunogenic after 1 dose - required 3 doses  
to mount an anti-DT response equal to 1 dose of conjugate

IS CARRIER PROTEIN RELEASED SLOWLY FROM THE CONJUGATE ?

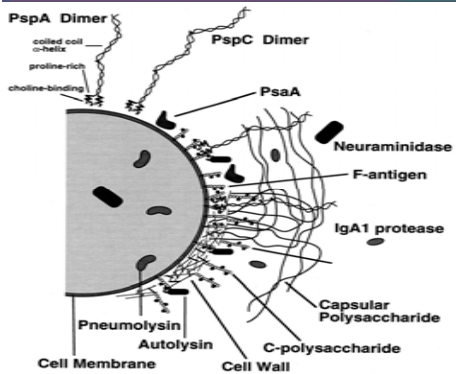
DOES CONJUGATION TO Vi PRESENT THE CARRIER PROTEIN MORE EFFICIENTLY TO IMMUNE CELLS?

NOTE: Physical structure is critical for this to work

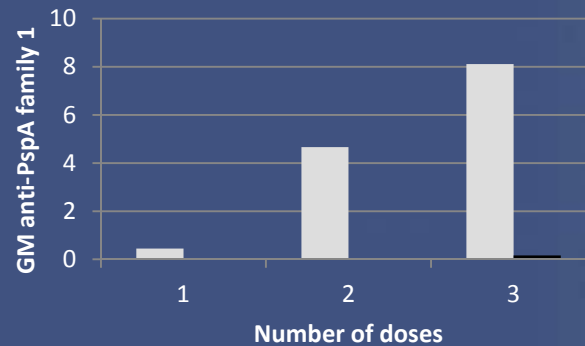


*Salmonella Typhi*  
Vi-DT conjugate

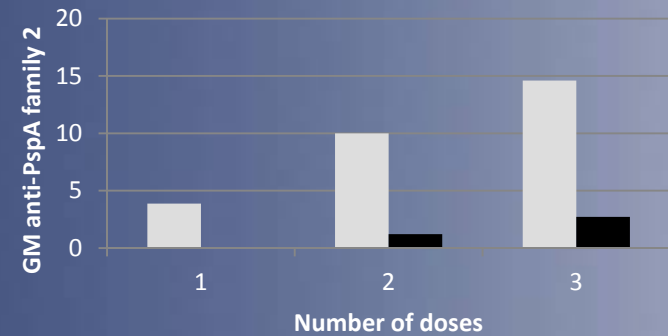
# Pneumococcal surface antigen A (PspA) – Vi conjugates



## Anti PspA family 1

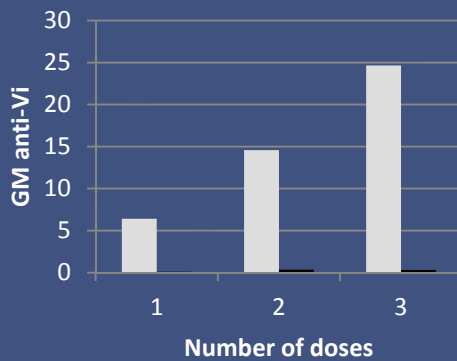


## Anti PspA family 2



White bars conjugates - Black bars un-conjugated PspA

## Anti-Vi



White bars conjugates - Black bars un-conjugated Vi

Conjugation of PspA (families 1 and 2) to Vi enhanced the response to both Vi and PspA

PspA is a suitable carrier protein.

Demonstrated PspA family specific protection in mouse intravenous challenge model.

Looking for a partner to co-develop this vaccine.

# Delivery

Vaccines only save lives after vaccination of susceptible individuals.

Vaccine development takes on real value only after introduction of the vaccine.

IVI through its DOMI program provided valuable disease incidence and burden data which assisted WHO in formulation of its recommendations for typhoid vaccination.

IVI is working on an investment case to assist GAVI in making decisions to fund typhoid vaccination.

**TYPHOID VACCINATION WILL SIGNIFICANTLY CONTRIBUTE TO IMPROVING THE HEALTH OF PEOPLE LIVING IN IMPOVERISHED CONDITIONS IN TYPHOID ENDEMIC AREA**

We need to continue working together to ensure that routine typhoid vaccination becomes a reality.



Thank you