



BILL & MELINDA
GATES *foundation*



TYPHOID VACCINES – UPDATE AND
PIPELINE REVIEW

Duncan Steele, PhD & Megan Carey, MPH
Bill & Melinda Gates Foundation

ASTMH Annual Meeting, Philadelphia. October 27, 2015

PREVENTING TYPHOID FEVER

Safe water

- Typhoid is a waterborne disease and the main preventive measure is to ensure the access to safe water

Food safety

- Contaminated food is a major vehicle for typhoid transmission

Sanitation

- Proper sanitation contributes to reducing the risk of transmission of diarrheal and enteric pathogens

Health education

- Health education is paramount to raise public awareness on all preventive methods

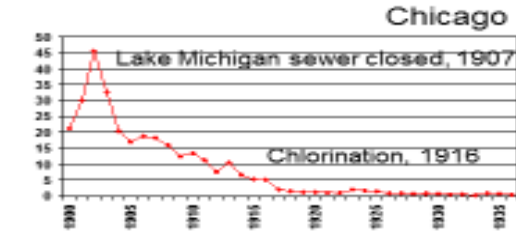
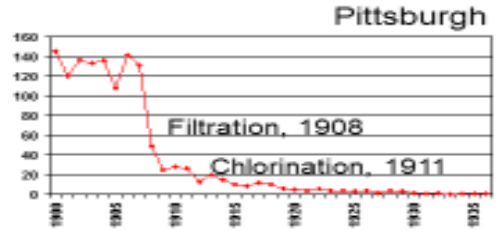
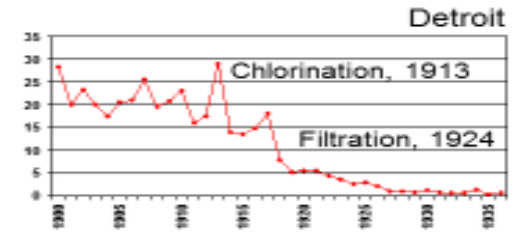
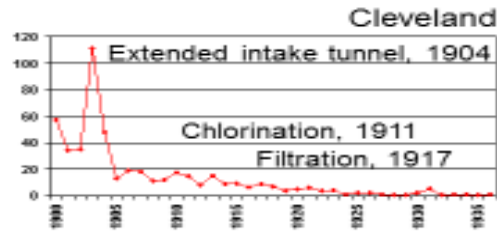
→ **These all remain as long-term preventive measures, especially in developing countries**

Vaccination

- Safe and efficacious vaccines are available

→ **Potential short- to mid-term solution in developing countries**

SAFE WATER



Typhoid Fever Trends (mortality per 100,000) in Four US Cities, 1900-36



IMPROVED SANITATION



FOOD SAFETY



LICENSED TYPHOID VACCINES: UNDER-UTILIZED

Ty21a live oral strain

- Enteric coated capsules (3 or 4 doses)
- Sachet formulation (liquid suspension) (3 doses)
- Licensed for use in persons over two years of age (liquid)



Purified Vi polysaccharide parenteral vaccine

- Single dose
- Licensed for use in persons over two years of age



CHARACTERISTICS OF CURRENT TYPHOID VACCINES

Characteristic	Live attenuated Ty21a	Vi capsular polysaccharide
Vaccine type	Live attenuated	Subunit
Composition	Chemically-mutated Ty2 strain of <i>S. Typhi</i>	Purified Vi capsular polysaccharide of the Ty2 <i>S. Typhi</i> strain
Immunogenic properties	<ul style="list-style-type: none"> ▪ Elicits mucosal IgA and serum IgG antibodies against O, H and other antigens, as well as cell-mediated responses ▪ No booster effect has been shown ▪ Not immunogenic in infants and toddlers* 	<ul style="list-style-type: none"> ▪ Elicits serum IgG Vi antibodies ▪ T-cell independent (no booster response)
Route of administration	Oral	Parenteral (subcutaneous or intramuscular)
Formulation	Enteric-coated capsules, or Liquid suspension (lyophilized vaccine + buffer mixed with water upon use)	Solution of 25 µg combined with buffer

CHARACTERISTICS OF CURRENT TYPHOID VACCINES

Characteristic	Live attenuated Ty21a	Vi capsular polysaccharide
Minimum age vaccine is licensed for use	Two years old for liquid formulation and five years old for capsule formulation	Two years old
Number of doses required for complete vaccine regimen	Three to four	One
Storage requirements	Requires storage at 2° to 8°C	Requires storage at 2° to 8°C
Shelf life in higher temperature	14 days at 25 °C	6 months at 37 °C 2 years at 22 °C
Safety/tolerability	High	High
Efficacy at 3 years (95% CI)*	51% (36%, 62%)	55% (30%, 70%)
Length of protection	At least 5-7 years	At least 3 years
Ability to induce herd protection	Documented ⁺	Documented [^]

W.H.O. TYPHOID VACCINE POSITION PAPER

RECOMMENDATIONS FOR THE TWO TYPHOID VACCINES

Relevant excerpts from WHO Position Paper (2008)

Two typhoid vaccines are currently recommended for use:

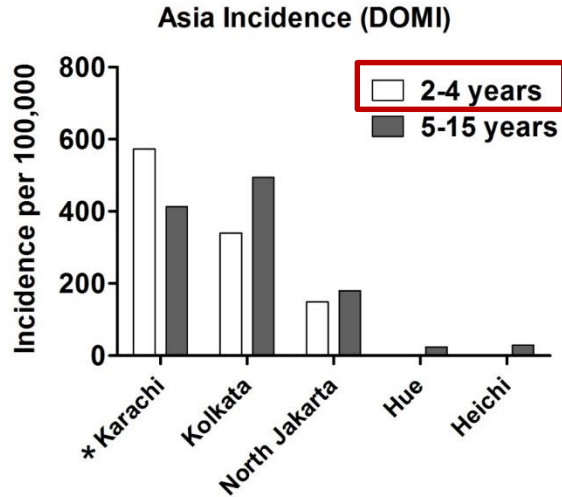
- an injectable polysaccharide vaccine based on the purified Vi antigen (known as Vi-PS vaccine) **for persons aged two years and above**
- a live attenuated oral Ty21a vaccine in capsule formulation **for those over five years of age**

Immunization of **school-age and/or preschool-age children** is recommended **in areas where typhoid fever in these age groups is shown to be a significant public health problem**, particularly where antibiotic-resistant *S.typhi* is prevalent. The selection of delivery strategy (**school or community-based vaccination**) depends on factors such as the age-specific incidence of disease, subgroups at particular risk and school enrolment rates, and should be decided by the concerned countries...

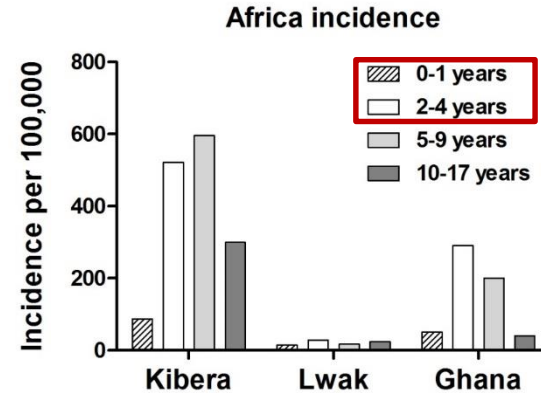
WHO recommends the use of the Vi-PS and Ty21a **vaccines to control endemic disease and for outbreak control**.

WHO further recommends that all typhoid fever **vaccination programmes should be implemented in the context of other efforts to control the disease**, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.

TYPHOID FEVER INCIDENCE IN ASIA AND AFRICA



- High incidence of typhoid fever in the region.
- Substantial regional variation in incidence.



- High incidence in urban slums; rates similar to those from Asia.
- Lower burden in rural children from Ghana (and Lwak, Kenya), compared to urban areas; regional differences

THE TIME FOR TYPHOID CONJUGATE VACCINES IS NOW...

New Vi-conjugate vaccines licensed locally:

- Bharat (Vi-tetanus toxoid), India
- Bio-Med (Vi-TT), India
- Lanzhou Institute BP (Vi-rEPA) pending in China

WHO position paper on production and evaluation of Vi-conjugate vaccines

GAVI position is awaiting WHO pre-qualification of a Vi-conjugate vaccine

Global spread of new antibiotic resistant clones (FQ)

Significant uncertainties about typhoid vaccines that must be addressed to inform policy

TYPHOID CONJUGATE VACCINE PIPELINE



1. Technology transfer from SBVGH
2. Technology transfer from IVI

VI-rEPA CONJUGATE VACCINE (DEVELOPED BY NIH)

A double-blind, placebo-controlled and randomized efficacy study was conducted in 2 to 5 year-old children in Vietnam

- 11,091 children were injected twice, 6 weeks apart, with the Vi-rEPA vaccine or saline placebo
- Efficacy at 27 months of active surveillance was 91%
- Efficacy at 46 months after additional 19 months of passive surveillance was 89%

A second study was conducted with 301 infants who received Vi-rEPA with routine childhood vaccines at 2,4, 6 months and Hib or Vi-rEPA at 12 months in Vietnam

- Vi-rEPA was safe in infants
- Induced protective anti-Vi levels, with robust GMTs
- Compatible with EPI vaccines and it can be used in infants.

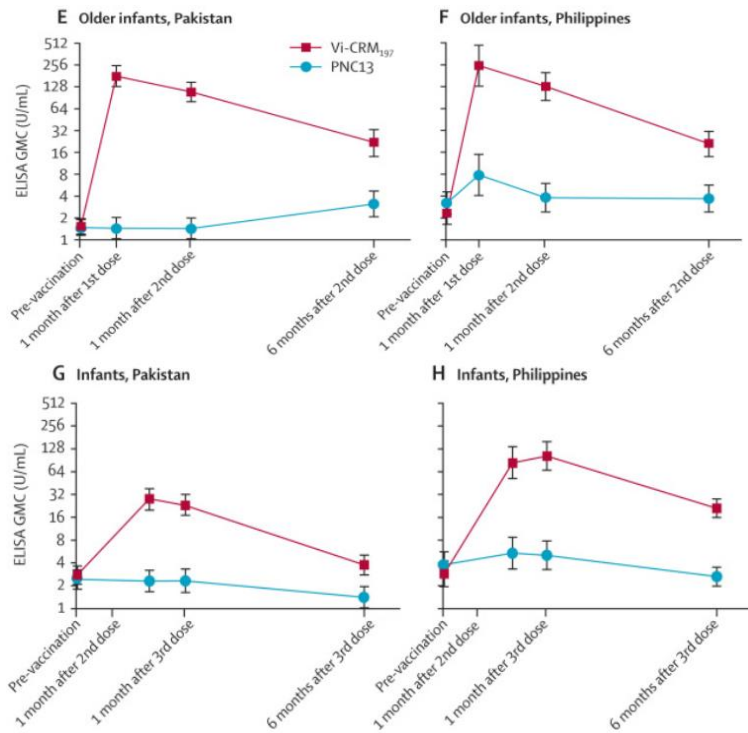
TABLE 3. EFFICACY OF VI-rEPA CONJUGATE VACCINE.

VARIABLE	VACCINE GROUP	PLACEBO GROUP	VACCINE EFFICACY (95% CI)* %	P VALUE†
Children who received two correctly labeled injections — no.	5525	5566	—	—
Children with typhoid fever — no.	4	47	91.5 (77.1–96.6)	—
Attack rate (cases/1000 children)	0.72	8.44	—	—
All children — no.‡	5991	6017	—	—
Children with typhoid fever — no.	5	56§	91.1 (78.6–96.5)	—
Attack rate (cases/1000 children)	0.83	9.31	—	—

This trial is the source of the only existing efficacy data for any typhoid conjugate vaccine, which has implications for future clinical development and regulatory pathways

Vi-CRM₁₉₇ CONJUGATE VACCINE (SBVGH & BIO-E)

Anti-Vi ELISA GMC of antibody by vaccine group, age, and country



- Randomized, observer-blind, age de-escalation Phase II study in Philippines and Pakistan
 - Adults aged 18-45 years, children 24-59 months, older infants 9-12 months, infants 6-8 weeks
- One dose significantly increased anti-Vi Ab concentration in adults, children and older infants
- In children and older infants, second dose of vaccine had no incremental effect on Ab titres,
- Ab concentrations increased significantly 6 mo. after vaccination, in all age groups

- Relatively modest responses in infants, observed decline in antibody titres overall similar to that seen with Vi-PS

- Bio-E working on Vi-CRM₁₉₇ construct following technology transfer from SBVGH

VI-DT CONJUGATE VACCINE CANDIDATES

Optimized **Vi production** during growth in a fermentor

Jang H, Yoon YK, Kim JA, Kim HS, An SJ, Seo JH, Cui C, Carbis R. Optimization of Vi capsular polysaccharide production during growth of *Salmonella enterica* serotype Typhi Ty2 in a bioreactor. *J Biotechnol* 2008/May; 135(1): 71-7.

Developed a novel Vi capsular polysaccharide **purification** process

Kothari S, Kothari N, Kim JA, Lee E, Yoon YK, An SJ, Jones C, Choe WS, Carbis R. A novel method for purification of Vi capsular polysaccharide produced by *Salmonella enterica* subspecies enterica serovar Typhi. *Vaccine* 2013;31(42):4714-9.

Developed an efficient high yielding **conjugation** process

An SJ, Yoon YK, Kothari S, Kothari N, Kim JA, Lee E, Kim DJ, Park TH, Smith GW, Carbis R. Physico-chemical properties of *Salmonella typhi* Vi polysaccharide-diphtheria toxoid conjugate vaccines affect immunogenicity. *Vaccine* 2011;29:7618-23

An SJ, Yoon YK, Kothari S, Kim DR, Kim JA, Kothari N, Lee E, Park TH, Carbis R. Immune suppression induced by Vi capsular polysaccharide is overcome by Vi-DT conjugate vaccine. *Vaccine* 2012;30:1017-1022

Production and Quality Control SOPs - developed training plan

Transferred technology to 4 manufacturers

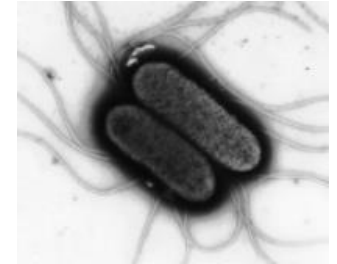
Shantha Biotechnics – cancelled the project

SK chemicals – clinical trials to begin soon

Biofarma – preclinical development almost complete

Incepta – early stages of preclinical development

Indian Immunologicals – pending



IVI PROCESS DEVELOPMENT (VI-DT)



biofarma

Process development:

High yielding antigen production

High recovery purification process

Scalable process compatible with cGMP production



SK chemicals

Technology Transfer:

High standards for quality, strict adherence to cGMP

Manufacturer(s) committed to low cost production and low margin sales

Developing Country Vaccine Manufacturers

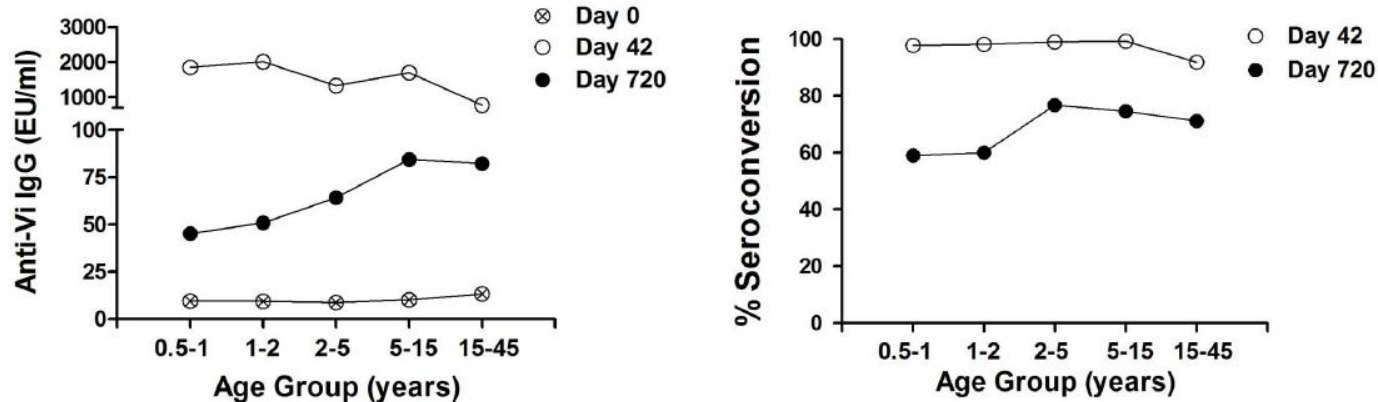
Manufacturers with capacity to WHO pre-qualify products



TYPHOID CONJUGATE VACCINE (VI-TT)

- Bharat Biotech vaccine licensed in India in 2013 on immunogenicity data
- Phase III - RCT in ages 2 - 45 year olds using licensed Typbar (Vi-PS) as an active comparator
- Open Label Trial in 6 months – 2 year olds
- Good immunogenicity responses across all age groups
- Post-licensure studies ongoing, including measles co-administration; evaluation of different dosing schedules; two years follow up for safety and immunogenicity data
- Human challenge study is ongoing at Oxford University to assess a clinical outcome for the vaccine

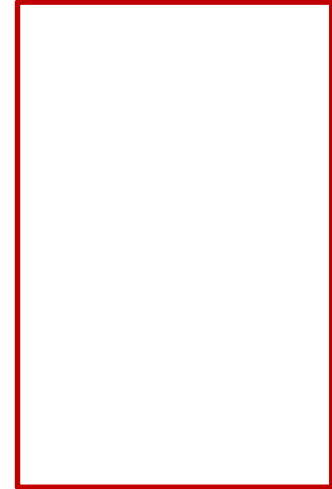
Immune Response Across Age Groups



VI-CONJUGATE VACCINE DEVELOPMENT & LICENSURE

Licensure on the basis of immunogenicity based on the Vi-rPA Vaccine Efficacy Data

1. Need a validated ELISA assay
 - Measures the concentration of anti-Vi IgG in human serum sample
2. Need a valid human reference standard to measure serum anti Vi-IgG
 - Will facilitate comparison of anti-Vi elicited from other manufactures to those of an experimental vaccine manufactured by the NIH (Vi-rPA) that has already undergone a clinical trial with efficacy outcomes
 - Allows for comparisons between laboratories
 - enables the comparison of antibodies elicited from other manufactures to those of Vi-rPA
 - Vi IgG antibody levels are currently being measured by investigators and referenced against arbitrarily-determined EU values assigned by each laboratory against its own in-house standard serum.



TYPHOID CHALLENGE MODELS

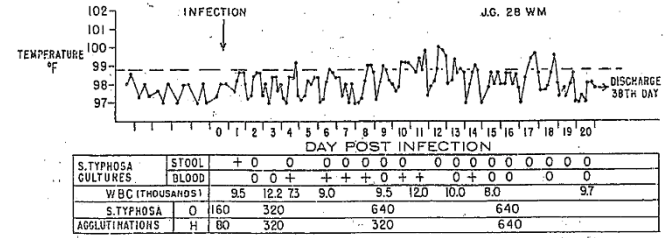
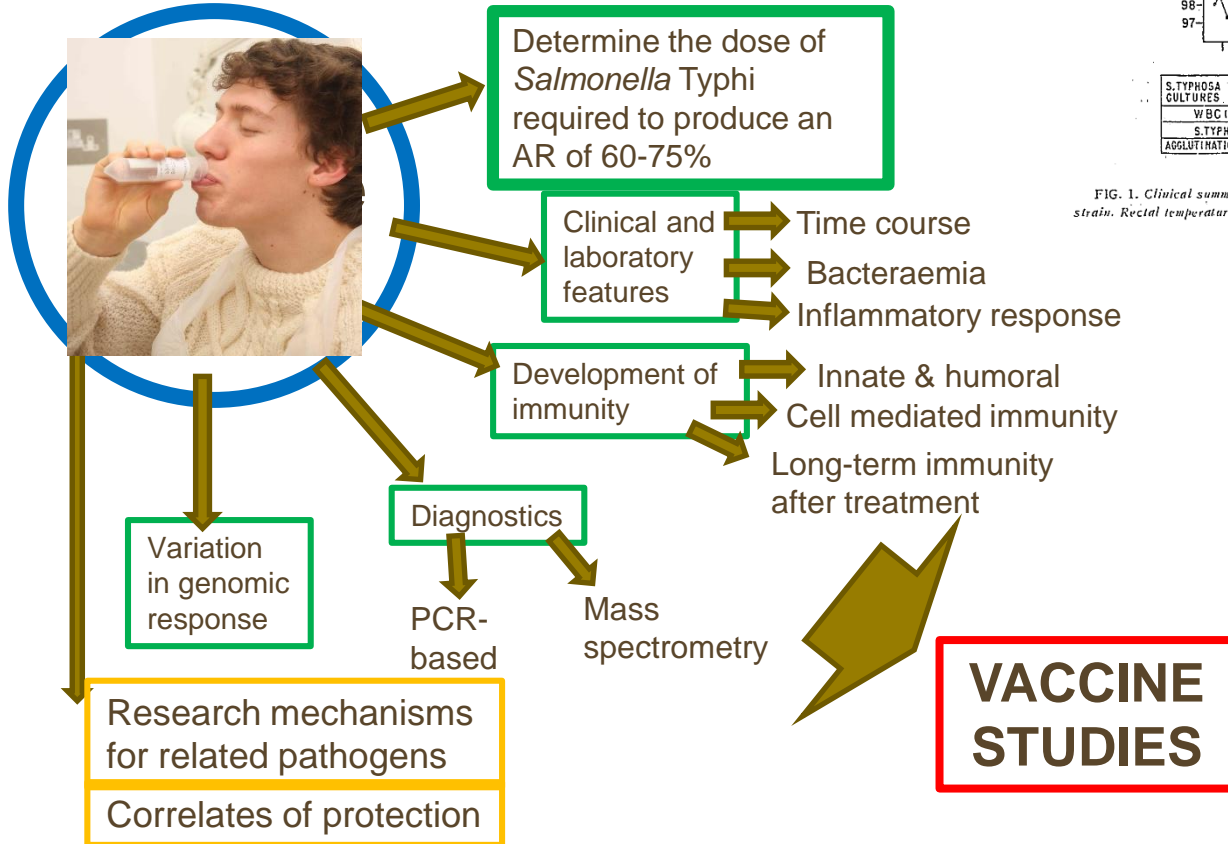
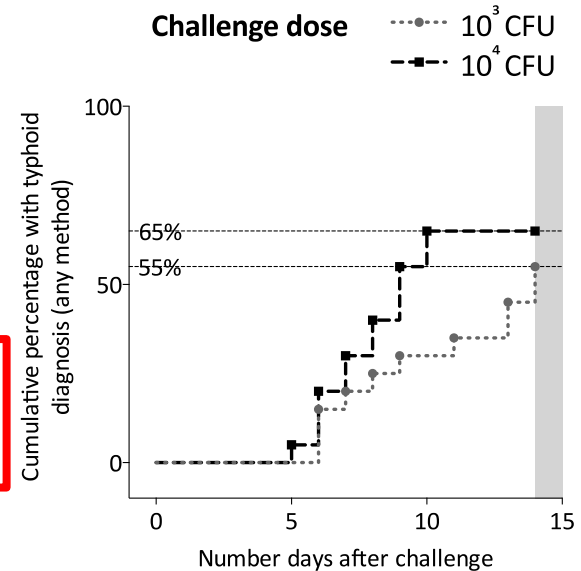


FIG. 1. Clinical summary of volunteer no. 9, J. G., after the ingestion of 10^8 viable *Salmonella typhosa* Quail's strain. Rectal temperatures are recorded.



EXPECTED ADDITIVE BENEFITS OF TYPHOID CONJUGATE VACCINES

- Improved level and duration of clinical protection
- Should boost Vi-primed immune memory (natural or plain Vi vaccine)
- Broader target age range (i.e., immunogenic in children <2 years)
- Potential for simplified delivery strategies (integration into routine schedule vs. school-based or campaign programs)
- Improved cost-effectiveness
- Improved vaccine acceptance and uptake

THANK YOU

