Typhoid Fever Vaccines

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Bangkok, Thailand
Outline

- Background: Typhoid disease burden estimates
- Background: Overview of typhoid vaccines
- Typhoid conjugate vaccine pipeline
- Knowledge gaps on typhoid conjugate vaccines
- Summary
Enteric fever: definition

• A systemic infection caused by *Salmonella enterica* serovar Typhi (Typhoid) or *Salmonella enterica* serovar Paratyphi A, B, and C (Paratyphoid)

• *Salmonella* belongs to the group of enterobacteriaceae that are aerobic and Gram-negative

• S. Typhi is transmitted via the oral-faecal route through contaminated food or water.

• Usually associated with poor sanitation and hygiene practices
History of Typhoid:
Typhoid Fever has impacted populations since antiquity

430–424 BC: plague of Athens killed one third of the population, including their leader Pericles. The balance of power shifted from Athens to Sparta, ending the Golden Age of Pericles and Athenian dominance in the ancient world.

Alexander the Great (356-323 BC) dies from typhoid fever in Babylon.

History of Typhoid

S. Typhi is observed and cultured for the first time in the early 1880’s

- The Widal agglutination test was described in 1896
- First used in municipal hospitals later that year (Johnston 1896) including the New York city Health Department (Guerard 1897)
# Typhoid fever burden estimates

<table>
<thead>
<tr>
<th>Source</th>
<th>Estimated Cases and Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivanoff et al (1994)</td>
<td>16.6 million cases and 580,000 deaths</td>
</tr>
<tr>
<td>Crump et al (2004)</td>
<td>21.6 million cases, 216,000 deaths</td>
</tr>
<tr>
<td></td>
<td>Highest incidence (&gt;100/100,000 per year) in south-central Asia and south-east Asia</td>
</tr>
<tr>
<td>Buckle et al (2012)</td>
<td>26.9 million cases (269,000 deaths)</td>
</tr>
<tr>
<td></td>
<td>Greatest increase in incidence in sub-Saharan Africa</td>
</tr>
<tr>
<td>IHME &quot;GBD 2013&quot;</td>
<td>2014 publication pending</td>
</tr>
<tr>
<td>IVI estimates</td>
<td>11.8-20.5 million cases and 129,000-223,000 deaths</td>
</tr>
<tr>
<td></td>
<td>2014 publication under review (Lancet Global Health)</td>
</tr>
<tr>
<td></td>
<td>Review by WHO IVIR-AC scheduled for Sept 2014</td>
</tr>
</tbody>
</table>

Adapted from Mogasale et al.
Estimated global burden of typhoid fever (2000 data)

Crump et al. WHO Bull 2004;82:346-53
Global Burden of Typhoid: Revised Estimates

Extrapolated from 1980s studies in Chile and South Africa

* Adjusted for blood culture sensitivity

Mogasale V, Maskery B, Ochiai LR, et al. Revisiting global burden of typhoid for policy considerations (Lancet Global Health; Under revision)
## Literature Review of Typhoid Risk Factors

<table>
<thead>
<tr>
<th>Significant risk factors</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Location/Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piped water supply at home</td>
<td>0.4</td>
<td>0.2-0.9</td>
<td>Darjeeling, West Bengal, India (Sharma, et al. 2009)</td>
</tr>
<tr>
<td>Latrine at home</td>
<td>0.5</td>
<td>0.3-0.8</td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>2</td>
<td>1.0-3.7</td>
<td>Son La province, northern Vietnam (Tran et al. 2005)</td>
</tr>
<tr>
<td>Drinking untreated water</td>
<td>3.9</td>
<td>2.0-7.5</td>
<td>Mekong delta, southern Viet Nam (Luxemburger et al. 2001)</td>
</tr>
<tr>
<td>Low economic level</td>
<td>2.9</td>
<td>1.5-5.3</td>
<td></td>
</tr>
<tr>
<td>Drinking unboiled water</td>
<td>4.3</td>
<td>1.3-14.5</td>
<td></td>
</tr>
<tr>
<td>Drinking unboiled water at home</td>
<td>12.1</td>
<td>2.2-65.6</td>
<td>Dhaka slum, Bangladesh (Ram et al. 2007)</td>
</tr>
<tr>
<td>Using foul-smelling water</td>
<td>7.5</td>
<td>2.1-25.4</td>
<td></td>
</tr>
<tr>
<td>Drinking water from a community tap</td>
<td><strong>0.03</strong></td>
<td><strong>0.003-0.331</strong></td>
<td>Karachi, Pakistan (Luby et al. 1998)</td>
</tr>
<tr>
<td>No municipal water supply in house</td>
<td>29.18</td>
<td>2.12-400.8</td>
<td>Semarang, Indonesia (Gasem et al. 2001)</td>
</tr>
<tr>
<td>Open or without drainage system of house</td>
<td>7.19</td>
<td>1.33-38.82</td>
<td></td>
</tr>
<tr>
<td>Unemployed or part time job</td>
<td>31.1</td>
<td>3.08-317.4</td>
<td></td>
</tr>
<tr>
<td>No toilet in the household</td>
<td>2.2</td>
<td>1.06-4.55</td>
<td>Jakarta, Indonesia (Vollaard et al. 2004)</td>
</tr>
<tr>
<td>Consumption of unboiled surface water outside the home</td>
<td>3</td>
<td>1.1-8.2</td>
<td>Samarkand Oblast, Uzbekistan (Srikantiah et al. 2007)</td>
</tr>
</tbody>
</table>
Control of Typhoid through Prevention

• Safe water
  • Typhoid fever is a waterborne disease and the main preventive measure is to ensure the access to safe water

• Food safety
  • Contaminated food is an important vehicle for typhoid fever transmission

• Sanitation
  • Proper sanitation contributes to reducing the risk of transmission of all diarrheal pathogens

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

• Vaccination
  • Safe and efficacious vaccines are available
Death Rate from Typhoid Fever in Philadelphia 1860-1936

Philadelphia Water Department Historical Collection
Downloaded from http://www.phillyh2o.org/filtration.htm

Civil war hospitals
Centennial celebrations
Household water filtration popularized
City water filtration installed

TOTAL DEATHS PER 100,000 POPULATION

1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935

1890s CENTRAL YEARS FILTERED
ENTIRE SUPPLY FILTERED 1909
ENTIRE SUPPLY CHLORINATED 1914
Global investments required for public health interventions

US $ 000s

Existing costs  Additional costs

EPI vaccines
Neonatal care
Nutrition Interventions
Water and sanitation

Bryce et al, (Lancet 2005)
Typhoid Vaccine Use in UK

1897 English bacteriologist Almroth Wright introduces a killed (heat-inactivated, phenol-preserved, whole-cell) typhoid vaccine in Britain.

1898-9 Trials in the Indian army produced excellent results and typhoid vaccination was adopted for the use of British troops serving in the Second Boer War (1899).


NB: whole-cell inactivated vaccine, one dose regimen, soldiers.
Typhoid Vaccine Use in USA

• **1909** typhoid vaccination starts in US Army

• **1911** typhoid vaccination required for entire US Army and Navy

The impact of typhoid vaccination in the US armed forces

- **World War I, 1917–1918**
  - 2,000 typhoid cases, 227 deaths (11.4% CFR)
  - 42 typhoid cases per 100,000 soldiers

- **World War II, 1941–1945**
  - 5 typhoid cases per 100,000 soldiers

Typhoid Vaccine Use in USA

- **1914** Typhoid vaccine first licensed for the U.S. general population

- **July 16, 1952** Heat-phenol inactivated typhoid vaccine by Wyeth licensed in US.

- **Dec 15, 1989** A live, oral typhoid vaccine (Ty21a, *Vivotif Berna* by Swiss Serum Institute) licensed in US.

- **Nov 28, 1994** Typhoid Vi polysaccharide inactivated injectable polysaccharide vaccine (Typhim Vi by Aventis Pasteur) licensed in US.

http://www.immunize.org/timeline/
WHO Position Paper on Typhoid Fever

In view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of 2 licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling endemic disease. In most countries, the high-risk groups and populations. Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended also for outbreak control.

Decisions on whether or not to initiate programmatic use of typhoid vaccines should be based on knowledge of the local epidemiological situation. Important information includes data on subpopulations at particular risk and age-specific incidence rates, as well as on the sensitivity of the prevailing S. Typhi strains to relevant antimicrobial drugs. Ideally, cost-effectiveness analyses should be part of the planning process.

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.

Typhoid fever vaccination may be offered to travellers to destinations where the risk of typhoid fever is high, especially to those staying in endemic areas for >1 month and/or in locations where antibiotic resistant strains of S. Typhi are prevalent.

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.
Global vaccination policy: WHO Position Paper 2008

• Programmatic use for endemic disease & outbreak control
• Vaccination of high-risk groups and populations
• Immunization of school-age and/or preschool-age children if a significant public health problem in these age groups
• Local factors required for decisions on programmatic use
  • Sub-populations at risk (to support risk-based strategy)
  • Age-specific incidence rates
  • Sensitivity of prevailing strains to relevant antimicrobials
  • Cost-effectiveness analyses
  • School enrolment rates etc.
Typhoid vaccines (licensed) overview

• **Vi polysaccharide vaccine (ViPS)**
  • IM/SC, 1 dose, 55-72% efficacy; 3 yrs duration of protection
  • **NOT licensed for <2 years of age**;
  • WHO prequalification (Typhim – 2011)

• **Ty21a**
  • oral, 3-4 doses, 35-67% efficacy; 7 yrs duration of protection
  • **NOT recommended for <5 yrs**;

• Programmatic feasibility and impact of vaccination demonstrated in several SEAR & WPR countries (mostly ViPS)
  • school-based & routine immunization delivery strategies
  • outbreak control in China, Fiji (2010, ViPS in cyclone-affected areas)

• **Future Gavi funding of conjugate vaccine** expected (Board decision in 2008)
Diseases of Most Impoverished Program (DOMI) Vi Effectiveness Trials

• Large scale effectiveness trials were conducted in slums in Kolkata, India and Karachi, Pakistan using Vi polysaccharide vaccine

• Studies were standardized, except the target population
  • Kolkata: 2 years and above
  • Karachi: 2-16 years
Results of the Effectiveness Trials

- Results from the two effectiveness trials showed differences in clinical protection for children aged 2-5 years

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Kolkata Protective Effectiveness</th>
<th>Karachi Protective Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4.9 years</td>
<td>82% (P&lt;.001; 95%CI: 58%,92%)</td>
<td>- 30% (95%CI: -183%,40%)</td>
</tr>
<tr>
<td>5.0-14.9 (Kolkata)</td>
<td>59% (P&lt;.05; 95%CI:18%,79%)</td>
<td>59%</td>
</tr>
<tr>
<td>5.0-16.0 (Karachi)</td>
<td>(P&lt;.05; 95%CI:9%,81%)</td>
<td></td>
</tr>
</tbody>
</table>
Results of the Effectiveness Trials

• Results on immunogenicity
  • For Kolkata, the small number of subjects under the age of 5 years bled at 6 weeks (N= 5) and 2 years (N= 3) after vaccination precluded meaningful analyses of this age group
  • For Karachi, results showed large number of children under the age of 5 showing no response after vaccination (7/41)
Summary

• Large clinical trial with a follow up period of 2 yrs
  • Difference in results based on clinical protection are unlikely to be different by chance

• Difference in design was the target population
  • Kolkata covered general population (2 and above) and attained 61% coverage
  • Karachi covered children (2 to 16) and attained 52% coverage

• Converted coverage (all age coverage)
  • Kolkata: 60%
  • Karachi: 22%
Summary

• The difference in the protection in the children less than 5 years of age is due to interruption of transmission (hence herd protection)
  • Potential mechanism of herd protection
    • Children under the age of 5 are usually at home under the care of parents
    • Children under the age of 5 usually consume food prepared at home and eat at home
    • If parents are protected, it is likely that the younger children are protected from transmission within household
Programmatic Use of Typhoid Vaccines

• Vi Vaccination Program for 2-5 Year Olds in Delhi, India
• Mass vaccination campaigns in several provinces and districts in China for school children and food handlers in mid-1990s
• Annual campaigns in Vietnam for 3-10 year old children in a limited number of high-risk districts since 1997
• Pondicherry and Fiji vaccination after outbreaks
• Sri Lanka vaccination campaigns for Internally Displaced people (IDPs) and food handlers
• Demonstration project in Nepal, Pakistan
Addressing the challenges: Typhoid conjugate vaccines

• Typhoid conjugate vaccine (ViCV): preparation of Vi polysaccharide covalently linked to a carrier protein
  • Vi antigen from S. Typhi or C. freundii
  • At least four carrier proteins

• Objectives of ViCV development (advantages over ViPS & Ty21a)
  • higher efficacy than the ViPS (>70% in endemic regions)
  • longer lasting protection (persisting > 3 years)
  • broader age coverage (i.e., immunogenic in infants)
# Typhoid conjugate vaccine pipeline

<table>
<thead>
<tr>
<th>No.</th>
<th>Manufacturer</th>
<th>Location</th>
<th>Technology Transfer Agreement</th>
<th>Product details</th>
<th>Clinical Dev’t Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bharat Biotech Int. Ltd. (BBIL)</td>
<td>India</td>
<td>Own R&amp;D (NIH technology)</td>
<td>Vi-TT</td>
<td>NRA Licensure in India</td>
</tr>
<tr>
<td>2</td>
<td>Shantha Biotechnics Ltd. (SBIL)</td>
<td>India</td>
<td>IVI</td>
<td>Vi-DT</td>
<td>Development stopped</td>
</tr>
<tr>
<td>3</td>
<td>Bio-Med Pvt. Ltd</td>
<td>India</td>
<td>Own R&amp;D (NIH technology)</td>
<td>Vi-TT</td>
<td>NRA Licensure in India</td>
</tr>
<tr>
<td>4</td>
<td>PT BioFarma</td>
<td>Indonesia</td>
<td>IVI</td>
<td>Vi-DT</td>
<td>Phase I clinical trial to start in 3Q 2015</td>
</tr>
<tr>
<td>5</td>
<td>Finlay Institute</td>
<td>Cuba</td>
<td>Unknown</td>
<td>Vi-DT</td>
<td>Phase I to start</td>
</tr>
<tr>
<td>6</td>
<td>Lanzhou Institute (CNBG)</td>
<td>China</td>
<td>US NIH</td>
<td>Vi-rEPA</td>
<td>NRA Licensure application submitted</td>
</tr>
<tr>
<td>No.</td>
<td>Manufacturer</td>
<td>Location</td>
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<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>7</td>
<td>SK Chemicals</td>
<td>S. Korea</td>
<td>IVI</td>
<td>Vi-DT</td>
<td>Phase I clinical trial will start in 4Q 2015</td>
</tr>
<tr>
<td>8</td>
<td>Incepta</td>
<td>Bangladesh</td>
<td>IVI</td>
<td>Vi-DT</td>
<td>Preclinical studies to start</td>
</tr>
<tr>
<td>9</td>
<td>Biological E</td>
<td>India</td>
<td>NVGH</td>
<td>Vi-CRM</td>
<td>Phase I clinical trial will start</td>
</tr>
<tr>
<td>10</td>
<td>EuBiologics</td>
<td>S. Korea</td>
<td>Own R&amp;D</td>
<td>Vi-CRM</td>
<td>Preclinical studies ongoing</td>
</tr>
<tr>
<td>11</td>
<td>DAVAC</td>
<td>Vietnam</td>
<td>Own R&amp;D</td>
<td>Vi-DT</td>
<td>Preclinical stage</td>
</tr>
<tr>
<td>12</td>
<td>Walvax</td>
<td>China</td>
<td>Own R&amp;D</td>
<td>Vi-TT</td>
<td>Preclinical stage</td>
</tr>
</tbody>
</table>
Vi-rEPA (Lanzhou Institute of Biological Products)

• Based on technology transfer from NIH
• Phase III data for adults, preschool and school aged children reviewed (not yet in public domain)
  • Data suggest immune response better in vaccine groups vs. controls
  • No efficacy trials in infants
• Licensure review by Chinese NRA ongoing (for use in persons >=2 y)
• Immunogenicity and safety studies planned in <2 years age group
Vi-CRM$_{197}$ (Biological E Limited)

• Early clinical testing by Novartis Vaccines Institute for Global Health (NVGH)
  • Phase I and II in European adults
  • 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) (Bhatta 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 weeks and 9-12 months 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 licensed to Biological E
  • Full clinical development programme planned
  • Interest expressed to apply for WHO PQ
Vi-TT (Bharat Biotech International Limited)

• Phase IIa/IIb study in 2-17 y: no difference in immune response in 1 vs 2 doses

• Phase III study
  • Cohort 1 >=6 months to <2 years (n = 327; no controls)
    • 98% protected (4-fold seroconversion)
  • Cohort 2 ≥2 years to ≤ 45 years (n ~340 per Vi-TT/ViPS arm)
    • 97% protection in Vi-TT arm vs 93% in ViPS arm (p=0.01).

• Licensed for single dose in >=6 m, children and adults
  • On average 30,000 doses per month sale in India, PMS safety evaluation (n ~3,000)
  • Interest expressed to apply for WHO PQ
## Typbar-TCV Product Characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Liquid Vaccine</td>
</tr>
<tr>
<td>Storage</td>
<td>$5^\circ C \pm 3^\circ C$</td>
</tr>
<tr>
<td>Dose volume</td>
<td>0.5 ml (Intramuscular injection)</td>
</tr>
<tr>
<td>Shelf life</td>
<td>24 months @ $5^\circ C \pm 3^\circ C$</td>
</tr>
<tr>
<td>O-Acetyl content (Hestrin)</td>
<td>NLT 0.085 ± 25% (25 µg of Vi Polysaccharide)</td>
</tr>
<tr>
<td>Vi Content</td>
<td>NLT 25 µg of Vi Polysaccharide</td>
</tr>
<tr>
<td>Free Vi-PS</td>
<td>NMT 20%</td>
</tr>
</tbody>
</table>
Typbar-TCV: phase IIa /IIb- Immunogenicity study data

- Single dose of 25µg Typbar-TCV is as immunogenic as two separated doses of 25µg or 15µg Typbar-TCV
# Typbar-TCV: Immune persistence data

## Open Label Trial

<table>
<thead>
<tr>
<th>Typbar-TCV</th>
<th>Day 0</th>
<th>Day 42</th>
<th>Day 720</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>307</td>
<td>307</td>
<td>220</td>
</tr>
<tr>
<td>GMT EU/ml (95% CI)</td>
<td>9.5 (9,10)</td>
<td>1937.4 (1785,2103)</td>
<td>48.7 (43,56)</td>
</tr>
<tr>
<td>Fold change</td>
<td>205</td>
<td>5.2</td>
<td></td>
</tr>
</tbody>
</table>

## Controlled Trial

<table>
<thead>
<tr>
<th>Typbar-TCV</th>
<th>Day 0</th>
<th>Day 42</th>
<th>Day 720</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>332</td>
<td>332</td>
<td>243</td>
</tr>
<tr>
<td>GMT EU/ml (95% CI)</td>
<td>10.4 (9.6,11.3)</td>
<td>1292.5 (1153,1449)</td>
<td>81.7 (73,92)</td>
</tr>
<tr>
<td>Fold change</td>
<td>124</td>
<td>7.8</td>
<td></td>
</tr>
</tbody>
</table>

## Typbar

<table>
<thead>
<tr>
<th>Typbar</th>
<th>Day 0</th>
<th>Day 42</th>
<th>Day 720</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>305</td>
<td>305</td>
<td>197</td>
</tr>
<tr>
<td>GMT EU/ml (95% CI)</td>
<td>11.6 (10.5,12.9)</td>
<td>411.1 (359,471)</td>
<td>45.8 (40,53)</td>
</tr>
<tr>
<td>Fold change</td>
<td>35</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>
Research scope to advance access to typhoid conjugate vaccines

• Field evidence to support country vaccine introduction
  • Individual and herd protection
  • Feasibility, acceptance of multiple injections
  • Cost effectiveness of various vaccine delivery strategies
  • Impact of vaccination in context of other control strategies (WASH, appropriate diagnosis and antimicrobial treatment etc.)

• Understanding impact of long-term carriers on disease burden (serologic or microbiological studies)

• Potential demonstration studies under consideration

• There may be opportunities to evaluate ViCV performance where a licensed vaccine is being used
Summary

• Typhoid continues to be a significant burden, mainly in developing countries of Southeast and South Asia
• Antibiotics resistance continues to be a public health threat
• Economic development (investment in infrastructure development) will significantly reduce typhoid incidence, but progress is very slow
• Vaccination programs using existing licensed vaccines have demonstrated impact of vaccines
• Conjugate vaccine candidates are expected to be available for public sector use in the next five years
• Concrete efforts from global health community, especially typhoid endemic countries is critical
Typhoid Fever: Research and Control Journey

- **1800**: Isolation of *S. typhi* organism (1880)
- **1850**: Widal Diagnostic (1896)
- **1900**: Typhoid immunization available
- **1950**: Development of heat-inactivated phenol-preserved whole-cell typhoid vaccine
- **2000**: Acetone-inactivated whole-cell typhoid vaccine (1960s)
- **2050**: Ty21a (live oral)
- **2100**: Better and improved vaccines?

**Key Events:**
- **1896**: Widal Diagnostic
- **1948+**: Chloramphenicol
- **1960s**: Acetone-inactivated whole-cell typhoid vaccine
- **1996**: Ty21a (live oral)

**Diagnosis and Treatment:**
- **1896**: Widal Diagnostic
- **1948+**: Chloramphenicol
- **1960s**: Acetone-inactivated whole-cell typhoid vaccine
- **1996**: Ty21a (live oral)

**Vaccines and Vaccination:**
- **1896**: Widal Diagnostic
- **1948+**: Chloramphenicol
- **1960s**: Acetone-inactivated whole-cell typhoid vaccine
- **1996**: Ty21a (live oral)

**Questions:**
- MDR
- Better and improved vaccines?
Thank you