Production capacity and supply of typhoid fever vaccines for developing countries

Rodney Carbis
Head Vaccine Development, IVI
Licensed Typhoid Fever Vaccines

Anti-typhoid vaccination in the United States Army, c. 1915.

Soldiers in a hospital on the Civil War battlefield, Georgia, scene of the Army’s worst typhoid epidemic in 1898.
1. Vi polysaccharide vaccine
Licensed for use in persons > 2 years of age

2. Live attenuated oral Ty21a
Licensed in persons 5 years of age and above.

3. Heat-inactivated phenol preserved
   • Very reactogenic due to LPS
   • Still licensed and used in some countries
Future vaccines

Vi conjugate
Dr John Robbins NIH

Exoprotein A (rEPA)

NHNHCO(CH$_2$)$_4$CONHNH

Spacer

Vi

Capsular Polysaccharide
Vi conjugate vaccine
Clinical trials

• In phase II trials high seroconversion rates after one dose and clear booster responses following the second dose.

• Randomized controlled phase III trial in Vietnam in children (2 - 5 years old).
  • 2 injections 6 weeks apart
  • 92% protection after 27 months (active surveillance)
**Future vaccines**

**Live attenuated candidates**

1. **CVD 908-htrA** with a mutation deletion in the htrA gene
   - CDV 909 derived from 908 but Vi positive (ACAMBIS/BERNA)

2. **χ4073** strain with a triple mutation deletion in the cya, crp, and cdt genes (Roy Curtis)

3. **Ty800** with a double mutation deletion in phoP and phoQ (AVANT)

4. **ZH9** a double mutation in aroC and ssaV genes (EMERGENT)
Live attenuated Ty21a

Derived from Ty2

- Developed in the early 1970s
- Non specific mutagenesis using nitrosoguanidine
- A large number of mutations including \textit{galE} gene and other genes responsible for the production of Vi
Clinical trials
Phase III trials in Egypt and Chile and Indonesia

- Three doses of enteric coated capsules provided 67% protection over 3 years and 62% over 7 years.

- Three doses of liquid formulation provided 77% protection over 7 years.

- The vaccine induced anti-Salmonella antibodies (O antigen) and a strong cell-mediated immune response.
Live attenuated Ty21a

Vivotif formulation

Contains \((2 \text{ to } 6) \times 10^9\) cfu of Ty21a

\((5 \text{ to } 50) \times 10^9\) non viable Ty21a

- 26 to 130 mg sucrose
- 1 to 5 mg ascorbic acid
- 1.4 to 7.0 mg amino acid mixture
- 100 to 180 mg lactose
- 3.6 to 4.4 mg magnesium stearate
Live attenuated Ty21a

Licensed in 56 countries

Produced by Berna Biotech - Switzerland
- Presented as phtallate-coated gelatin capsules
- A liquid formulation is also available (with sachet and buffer)
- Administered as three doses 2 days apart
Vi capsular polysaccharide vaccine

Licensed in more than 92 countries

Producers include
- Sanofi Pasteur - Typhim Vi
- GlaxoSmithKline - Typherix
- Bharat Biotech India - Typhbar Vi
- Bio Med India - Typho Vi
- Finlay Institute Cuba - Vax-TyVi
- IVAC Vietnam
- 6 producers in China including
  - Lanzhou Institute
  - Chengdu Institute
Vi capsular polysaccharide vaccine

Clinical trials
• Single subcutaneous or intramuscular dose of 25μg of purified Vi polysaccharide
• Randomized controlled trials
  - 72% protection 17 months post vaccination in Nepal
  - 65% protection 21 months post vaccination in South Africa
  - Studies in China using locally made vaccine show similar results
• Vi polysaccharide is a T-cell independent antigen and as such is poorly immunogenic in infants
• Antibody responses are not boosted by additional doses
Features of Vi vaccine
Suitability for public health

Single dose

Highly temperature stable
Physicochemical characteristics unchanged after 6 months at 37°C

Production technology relatively simple

High yields - No supply problems

Affordable to public health programs
Public sector purchases for less than 50 cents per dose

Large number of manufactures
Competition keeps price affordable for public sector purchases
Vi capsular polysaccharide vaccine

Fermentation

Inactivation

Vi Capsular Polysaccharide Purification

Sterile Filtration

Formulation
Final yield 100mg/litre of fermentation broth.

Equivalent to 4,000 doses per litre.

1000 litre fermentation 4,000,000 doses
• The WHO recommends that the immunization of school aged children be undertaken wherever the control of the Typhoid fever is a priority.
Where is Typhoid Fever a problem?

- High endemicity
- Medium endemicity
- Sporadic outbreaks

622 per 100,000 per year
110 per 100,000 per year
Pakistan:
Sanofi, GSK, and Berna all market vaccine with annual sales of approximately 70,000 doses at USD 6.00 per dose.

India:
Vaccine is produced at well under USD 1.00 per dose. Large numbers of doses are being sold in India but all to the private market.
Typhoid Vaccine Market Share

60 million doses per annum

- **Sanofi**: 46%
- **Local manufacturers**: 42%
- **Berna**: 5%
- **GSK**: 7%
- **Local manufacturers**: 42%
- **Sanofi**: 46%
Both currently licensed vaccines have good safety profiles and have shown reasonable protective efficacy.

Neither has been widely adopted as a routine public health tool in developing countries with endemic typhoid fever.
## Population statistics

<table>
<thead>
<tr>
<th>Country</th>
<th>Population 2004</th>
<th>Annual no. of births</th>
<th>Approximate no. of children ≤ 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>1,087,000,000</td>
<td>26,000,000</td>
<td>260,000,000</td>
</tr>
<tr>
<td>Indonesia</td>
<td>220,000,000</td>
<td>4,500,000</td>
<td>45,000,000</td>
</tr>
<tr>
<td>Pakistan</td>
<td>155,000,000</td>
<td>4,729,000</td>
<td>47,290,000</td>
</tr>
<tr>
<td>School aged children (6 -12 years)</td>
<td>200,000,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Developing Country Producers
Could produce and market vaccine at affordable prices

<table>
<thead>
<tr>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bharat Biotech</td>
<td>Producing and distributing vaccine</td>
</tr>
<tr>
<td>India</td>
<td>Licensed in several countries</td>
</tr>
<tr>
<td>BioMed</td>
<td>Producer and selling in India</td>
</tr>
<tr>
<td>India</td>
<td></td>
</tr>
<tr>
<td>Shantha</td>
<td>Developing a Vi vaccine</td>
</tr>
<tr>
<td>India</td>
<td></td>
</tr>
<tr>
<td>BioFarma</td>
<td>Developing a Vi vaccine</td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
</tr>
<tr>
<td>IVAC</td>
<td>Producer supplying Vietnamese market</td>
</tr>
<tr>
<td>Vietnam</td>
<td></td>
</tr>
<tr>
<td>Chinese Producers</td>
<td>Several producers mainly supplying private market in China</td>
</tr>
</tbody>
</table>
Age distribution of typhoid Fever cases identified at a diagnostic referral center in Dhaka, Bangladesh (n=391)

<table>
<thead>
<tr>
<th>Age</th>
<th>% of Isolates</th>
<th>Cumulative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0~5 mo</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>6~12 mo</td>
<td>8.7</td>
<td>9.5</td>
</tr>
<tr>
<td>13~24 mo</td>
<td>17.4</td>
<td>26.9</td>
</tr>
<tr>
<td>25~36 mo</td>
<td>15.3</td>
<td>42.2</td>
</tr>
<tr>
<td>37~48 mo</td>
<td>12.3</td>
<td>54.5</td>
</tr>
<tr>
<td>5~9 yr</td>
<td>24.0</td>
<td>78.5</td>
</tr>
<tr>
<td>10~19 yr</td>
<td>13.0</td>
<td>91.6</td>
</tr>
<tr>
<td>&gt; 20 yr</td>
<td>8.4</td>
<td>100</td>
</tr>
</tbody>
</table>

DOMI Results

Incidence of Culture-Confirmed Typhoid Fever

<table>
<thead>
<tr>
<th>City</th>
<th>Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karachi</td>
<td>573</td>
</tr>
<tr>
<td>Kolkata</td>
<td>494</td>
</tr>
<tr>
<td>North Jakarta</td>
<td>149</td>
</tr>
<tr>
<td>Hue</td>
<td>24</td>
</tr>
<tr>
<td>Hechi</td>
<td>29</td>
</tr>
</tbody>
</table>
Conjugate vaccine introduction

• Justification for a Vi conjugate vaccine
  - Vaccination of children <2 years of age
  - Better responses in 3 - 5 years olds (and older children) compared with Vi polysaccharide vaccine
  - Vaccination with other EPI vaccines
• Will take up to 7 years to license
• Meanwhile 21 million cases of typhoid fever resulting in excess of 200,000 plus deaths
• Vi production and capacity must be established before conjugate can be produced
• It makes sense to establish a public sector market with Vi now and introduce Vi-conjugate when it becomes licensed
Vi conjugate development at IVI

Diphtheria toxoid

Spacer

NHNHCO(CH$_2$)$_4$CONHNH

Vi

Technology assistance from NIH
Thank you

Vaccines don't save lives
Vaccination does