Impact of Typhoid Conjugate Vaccine Use on Global Disease Burden

ASTMH symposium 126 - Typhoid Fever: the accelerated agenda to deliver conjugate vaccines

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Disclaimer

Complying with CME accreditation guidelines

- The speaker is employed by Novartis Vaccines Institute for Global Health (Siena, Italy) and receives salary and incentives from Novartis.

- NVGH, in partnership with Biological E Ltd (Hyderabad, India), is developing a typhoid conjugate vaccine, Vi-CRM$_{197}$.

- Concepts presented do not necessarily represent the official position of Novartis Vaccines Institute for Global Health nor Biological E Ltd.
Typhoid disease burden

*Current global distribution estimates*

![Map of typhoid incidence](image)

*Figure 3: Typhoid incidence in low-income and middle-income countries (risk-adjusted and corrected for blood culture sensitivity)*

From Mogasale, Lancet 2014
Typhoid disease burden

*Trends in global estimates; numbers increase with population*

Compiled from Edelman, Rev Infect Dis 1986
Crump, Bull WHO 2004
Buckle, J Global Health 2012
IHME, GBD database
Mogasale, Lancet 2014

Global typhoid fever burden

Year of estimate

Compiled from Edelman, Rev Infect Dis 1986
Crump, Bull WHO 2004
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Typhoid disease burden

Estimations are not easy

- Data gaps in epidemiology and surveillance

- Incidence differs by
  - region, country and municipality
  - degree of industrialization
  - population and age

- Prevention in long & short term via
  - Safe water & sanitation
  - Food safety
  - Health education
  - Vaccination
Impact of improved water supply
On typhoid disease burden (Philadelphia 1860-1936)
Impact of simple water systems & latrine use
On typhoid disease burden (Sarawak, Malaysia 1963-2002)

Typhoid Incidence rate (per 100,000 pop)

Year

(B)

implementaiton

44% coverage

97% coverage

Impact of inactivated whole-cell vaccine
On typhoid disease burden (in US Navy admissions)

Modified from Cook, Am J Public Health 1934
Impact of inactivated whole-cell & Vi PS vaccines
On typhoid disease burden  (Cuba 1980-2007)

Population: 10-13-16 yr
Schedule: one dose Vi PS

Modified from mediccreview.medicc.org/articles/mr_56.pdf
Impact of Vi polysaccharide vaccine (1)
On typhoid disease burden (Southwest China, Guilin Guangxi Province)

Population: school aged kids & high risk
Schedule: one dose
Coverage rate (targeted): ~65% & ~82%
Impact of Vi polysaccharide vaccine (2) 
On typhoid disease burden (Northwest Vietnam)

Population: kids 3-10 yr
Schedule: one dose
Coverage rate (targeted): 70 - 90%

From Khan, Expert Rev Vaccines 2010
Estimating impact of Vi conjugate vaccines

Role for mathematical modelling

- Models validated against Vi polysaccharide vaccine data
- Vaccine impact relative to vaccine characteristics

<table>
<thead>
<tr>
<th>Vi polysaccharide reality</th>
<th>Vi conjugate vaccine expectation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensed for &gt; 2 years of age</td>
<td>Delivery with EPI from 9 months</td>
</tr>
<tr>
<td>Seroconversion 85-95%</td>
<td>Seroconversion 85-95% including infants</td>
</tr>
<tr>
<td>Efficacy ~65%</td>
<td>Efficacy &gt;85%</td>
</tr>
<tr>
<td>Duration of protection ~3 years</td>
<td>Duration of protection ~10 years</td>
</tr>
<tr>
<td>Antibody response not boostable with possible immune tolerance</td>
<td>Boostable antibody response</td>
</tr>
</tbody>
</table>

- (type of immunity, carriers, herd immunity, typhoid endemicity, population coverage, other interventions, etc)
Estimating impact of Vi conjugate vaccines

Some key vaccine parameters used as input in the models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Yale model</th>
<th>NVGH model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vi PS vaccine efficacy</td>
<td>80% (68% over 1st year)</td>
<td>72%</td>
</tr>
<tr>
<td>Vi PS protection</td>
<td>36 months (exponential decay)</td>
<td>34 months (truncated normal distribution)</td>
</tr>
<tr>
<td>Vi conjugate vaccine efficacy</td>
<td>95.6%</td>
<td>96%</td>
</tr>
<tr>
<td>Vi conjugate protection</td>
<td>230 months (exponential decay)</td>
<td>85 months (truncated normal distribution)</td>
</tr>
<tr>
<td>Population</td>
<td>Vellore, India</td>
<td>Kolkata, India Dhaka, Bangladesh</td>
</tr>
<tr>
<td>Duration natural immunity</td>
<td>104 weeks</td>
<td>160 months clinical 800 months sterile</td>
</tr>
</tbody>
</table>

- Vaccination scenarios: which, who, when, where
Modeling the “which” – vaccination at 6 years

Longer duration vaccine gives bigger impact

Vi polysaccharide  Vi conjugate

Compiled from Pitzer, PLoS Neg Trop Dis 2014
Saul, unpublished
Modeling the “who” – routine vs campaign only

*Campaign gives rapid & big reduction, but also pronounced rebound*

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**Routine**

![Graph showing typhoid cases per week for routine vaccination](image1)

- @ 6 yr

**Campaign**

![Graph showing typhoid cases per week for campaign vaccination](image2)

- @ 6-15 yr

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**Typhoid cases (per week)**

- No vaccination
- Population direct effect
- Overall effect

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Compiled from Pitzer, PLoS Neg Trop Dis 2014

Saul, unpublished
Modeling the “when” – 9 mo + booster

Booster can give sustained effectiveness

9 months only

9 month + booster @ 6-7 yr

Model output not published

Typhoid cases (per week)

Year

No vaccination
Population direct effect
Overall effect

Compiled from Pitzer, PLoS Neg Trop Dis 2014
Saul, unpublished
Modeling the “where” – Kolkata vs Dhaka

Endemicity matters for vaccine impact

Kolkata, India

Dhaka, Bangladesh

@ 9 mo

@ 6 yr

Saul, unpublished

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Outcomes of mathematical modeling

Positive outlook on typhoid disease burden

- Vi conjugate vaccines give bigger impact than Vi polysaccharide
- Vaccine campaigns give rapid and big reduction in cases but, with rebound
- Routine + booster vaccination give best sustained effectiveness
- Age of vaccination may impact disease reduction, especially when disease is present in youngest age groups, and should match risk
- Vaccine impact will vary dependent on disease heterogeneity

Vi conjugate vaccine implementation reduces transmission but on its own will not eliminate typhoid!
Vi conjugate impact on typhoid disease burden

Extrapolating from Vi polysaccharide in Thailand, China and Vietnam

Global typhoid fever burden

Year of estimate

Vi conjugate WHO PQ and introduction

>25-43% in 1st year

>90% in 10 years

Compiled from Edelman, Rev Infect Dis 1986
Crump, Bull WHO 2004
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IHME, GBD database
Mogasale, Lancet 2014
Vi conjugate impact on typhoid disease burden

Towards elimination
Vi conjugate impact on typhoid disease burden
Towards elimination

- Better epidemiology especially in Africa
- Vi conjugate vaccine
  - Field data
  - Sufficient supply
  - Appropriate policy
  - Adequate coverage
- Attention to
  - Carriers
  - Rebound effect of vaccination
  - Co-infections (ie, paratyphoid)
- Improved WASH

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