Multiple Modalities to Explore
Typhoid among Children:
implication in vaccination policy

Samir K Saha
Child Health Research Foundation
&
Dhaka Shishu Hospital
~150 million people — 7th most populous country in the world

Population density ~2,000 persons/square kilometer — Highest among any country

- Global mean 42 persons/km²
- Per capita income: US$840

Prior Antibiotic – Community and Hospital

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before coming to hospital</td>
<td>32%</td>
</tr>
<tr>
<td>At hospital, prior to specimen collection</td>
<td>20%</td>
</tr>
<tr>
<td>Overall cases without prior antibiotic</td>
<td>48%</td>
</tr>
</tbody>
</table>
Surveillance for Invasive Bacterial Infections – Multiple Modalities

• Multicentre laboratory based surveillance in Dhaka city
• Multicentre hospital based surveillance – Urban and Rural
• Population based surveillance in a rural community
• Population based surveillance in an urban slum
Multicentre Laboratory Based Surveillance in Dhaka City (1994 – 2011)

Out patient based diagnostic centers
- Expensive private facilities
- Cases referred by senior pricey practitioners
- Higher SES
Multicentre Laboratory Based Surveillance in Dhaka City (1994 – 2011)

Total Blood Culture = 74,210

Positive Cases = 6,678 (9%)

Salmonella Typhi = 4,111 (62%)
Hospital Based Surveillance -
Network of 4 Hospitals (1,055 beds)

- 60 Km from Dhaka
- 80 Paediatric Beds

- 300 Km from Dhaka
- 200 Paediatric beds

- Dhaka
- 175 Paediatric Beds

- SSF, Dhaka
- DSH
- KWMCH
- COMSH

Dhaka Shishu Hospital
600 Paediatric Beds

WHO Sentinel Site

Rural Hospital

Chittagong
Multicentre Hospital Based Surveillance for invasive bacterial diseases

Screen babies of 2-59 months

IF MEET INCLUSION EXCLUSION CRITERIA

ELIGIBLE
Consent taken

BLOOD COLLECTION

ENROLLED

CULTURE
Multicentre Hospital Based Surveillance for Invasive Bacterial Diseases – 3 urban hospitals

Number of blood cultures (18,652)
- 495 S. typhi
- 64% of all isolates

Predominance of S. typhi
- True for other hospitals

All admitted cases
- More severe cases than community patients in lab based surveillance
Multicentre Hospital Based Surveillance for Invasive Bacterial Diseases – Rural hospital

- Total blood culture – 4,203
- Relatively low rate of isolation – 42% of all isolate
- Relatively low prevalence
Mirzapur, Rural Bangladesh

POPULATION BASED FIELD SITE
Integrated Rural Field Site

- Mirzapur
  - 63 kilometers north of Dhaka city
  - Population: 400,000
- Health facilities:
  - Kumudini Hospital (750 beds)
    - ~120 pediatric patients at OPD daily
    - >500 patients a day
    - Pediatric ward of 80 beds
  - Upazilla Health Complex (31 beds)
Distribution of Blood Culture in Rural Bangladesh

Frequency of Isolates

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>144,000</td>
</tr>
<tr>
<td>Total enrolled</td>
<td>11,439</td>
</tr>
<tr>
<td>Episodes with temp ≥100.4°F</td>
<td>3,978</td>
</tr>
<tr>
<td>Blood Culture done</td>
<td>3,724</td>
</tr>
</tbody>
</table>
## Age-specific Incidence of typhoid fever <5 children in rural Bangladesh

<table>
<thead>
<tr>
<th>Age groups (months)</th>
<th>Culture confirmed cases</th>
<th>Typhoid incidence/ per 100,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 11</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>12 – 23</td>
<td>3 (12.5)</td>
<td>94</td>
</tr>
<tr>
<td>24 – 35</td>
<td>6 (25)</td>
<td>145</td>
</tr>
<tr>
<td>36 – 47</td>
<td>13 (54.2)</td>
<td>304</td>
</tr>
<tr>
<td>48 – 59</td>
<td>2 (8.3)</td>
<td>64</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>24 (100)</strong></td>
<td><strong>151</strong></td>
</tr>
</tbody>
</table>
Population Based Surveillance in Urban Slum
Population Based Surveillance in Urban Slum

Active surveillance all age group

Fever ≥38°C – blood culture

Total blood culture – 888
Total positive – 65 (7%)
*S. typhi* – 49 (75%)

Predominant cause of bacteraemic fever

Incidence

<5 years – 19 episodes/1000 person-years
≥5 years – 4 episodes/1000 person-years

Brooks et al 2005
The specter of anti-microbial resistance

DO WE KNOW THE DYNAMICS?
Treatment of Typhoid Fever

- **1st line of Antibiotic**
  - Amoxycillin
  - Chloramphenicol
  - Cotrimoxazole

- **Problem since 1990s**
  - Slow epidemic of multi-drug resistant *S. Typhi* in the subcontinent

- **Concern for the public health practitioners**
- **Confusion between clinicians and microbiologists**

- **2nd line of antibiotic**
  - Ceftriaxone - Expensive
  - Ciprofloxacin – Widely Used

Saha et al. 1995
Trend of Drug Resistance ‘94-’11
(N=5,937)

- Progressive increase in relative resistance to ciprofloxacin
  - Delay in clinical response
  - Treatment failure
  - Recurrences

Increase in Nalidixic Acid Resistance

Emergence of Highly Cipro-Resistant S. Typhi: Molecular Basis of Resistance

- Highly ciprofloxacin resistant S. Typhi
  - MIC 512 µg/ml
  - Double mutation at point 83 and 87 of gyrase genome
  - Contrast to “No mutation” in sensitive strains

Saha et al. J. Clin Microbiol 2006
Financial Implications of Drug Resistance

- High prevalence of MDR and NalidRX
- Increasing trend of isolation at hospital
  - Hospitalization lead to 10 times increase in direct cost ($22-29 Vs $172-286)
    - Mean income of typhoid cases - $73
  - Indirect cost – absence from the business, food for attendants, missing schools, etc.
Improved Living Conditions – sanitation, hygiene, piped water and so on

WHAT COULD BE THE POSSIBLE IMPACT ON TYPHOID?
### Comparative Prevalence of Typhoid in Urban and Rural Bangladesh

<table>
<thead>
<tr>
<th></th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among blood cultures - Hospital</td>
<td>2.7%</td>
<td>0.80%</td>
</tr>
<tr>
<td>Among blood cultures - Community</td>
<td>5.4</td>
<td>0.64%</td>
</tr>
<tr>
<td>Among isolates - Hospital</td>
<td>64%</td>
<td>41%</td>
</tr>
<tr>
<td>Among isolates - Community</td>
<td>75%</td>
<td>56%</td>
</tr>
<tr>
<td>Incidence/100,000</td>
<td>1,900</td>
<td>151</td>
</tr>
</tbody>
</table>

#### Rate of Urbanization in Bangladesh

![Graph showing the rate of urbanization in Bangladesh from 1951 to 2015](image)
Immunization against Typhoid

PERSPECTIVE FOR BANGLADESH AND BEYOND
Typhoid: Dogma of Recent Past

The disease is not prevalent among Preschool Children
Even if it is there, the disease episodes are benign
Age Group Distribution of Typhoid Cases (N= 5,937)

- Maximum number of cases in 2\textsuperscript{nd} year of life
- Not in agreement with the common belief of age distribution
Age Group Distribution (N= 5,937) – impact on typhoid vaccination policy

- **Conjugate vaccine can give 98% coverage**
- Conjugate vaccine needed for this group
- *Adapted recommendation for vaccination*
- *Original recommendation for vaccination*

- Existing vaccine not immunogenic in 23% of cases
- Conjugate vaccine needed for this group
- Conjugate vaccine can give 98% coverage

- **Percentage**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Original Recommendation for Vaccination</th>
<th>Adapted Recommendation for Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6m</td>
<td>0.8</td>
<td>7</td>
</tr>
<tr>
<td>0-12m</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>0-24m</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>0-36m</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>0-48m</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>0-60m</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>0-9y</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>0-19y</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>All age</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Typhoid in Early Age

IS IT REALLY SEVERE IN YOUNGER AGE GROUP?
Magnitude of S. Typhi bacteraemia

- Previous concept: Less severe in young infants?
  - High magnitude of bacteremia
  - Facility based study
    - Care seeking behavior
    - Access to health
  - We dealt with sicker children
- Severity in young children is no less

Saha et al PIDJ, 2000
Duration of Hospital Stay by Age Group

- Similar duration of hospital stay irrespective of age group
So we can not just escape the children

THESE ARE NOT THE POPULATION WE ARE LOOKING FOR
What needs to be done to prevent Typhoid

IMPROVED SANITATION AND IMMUNIZATION
Highest Price Tag for Child Survival

WATER AND SANITATION
Impact of Immunization is Straight Forward

• Bangladesh has Few Things to be Proud
  – Our Immunization Program
  – a success story e.g. near disappearance of Tetanus, Diphtheria, Polio, Hib, etc.

• In the process of introducing Pneumo vaccine
Issues with Typhoid Vaccines – Polysaccharide vs Protein Conjugated Vaccine

When conjugation technology is available for last 3 decades
Why the Uncertainty about Conjugate Vaccine for Typhoid?

- Disproportionately affects the people of developing countries
- No dedicated group to translate the typhoid research to public policy. As there is no donor!!
- Industries are not interested
- Minimal commercial value
- Possibility of market failure
New Hope in Preventing Typhoid
Thank You
Are we too much focused to our own agenda?

HOPE TO GET BACK THE PERIPHERAL VISION SOON
Expectations from this Meeting

• Bangladesh will be part of Global Health Work of UoT focusing on
  – Infectious Diseases
  – Translation of Science to Public Policy
WE DIDN’T INTEND TO DO ANY RESEARCH ON TYPHOID SPECIFICALLY

Donor Driven Research
Key Issues for this Talk

• Child Health
• Infectious Diseases
• Typhoid
• Surveillance
• Vaccines
Illogical Distribution of Technologies
Why the typhoid issue at Toronto?

DIDN’T WE ERADICATE TYPHOID YEARS AGO?

S. Typhi cases per year in Ontario, 2002-2007

Morris et al. 2009
Typhoid Travels Across the World

1,503 Typhoid cases in UK, 2006-09

![Bar chart showing typhoid cases in England, London, Tower Hamlets, and Newham.]

227 Typhoid Cases in Japan, 2005-08

- Japan: 16%
- South Asia: 56%
- SEA: 21%
- Central & South America: 1%
- Africa: 1%
- Oceania: 1%
- Unspecified: 4%

![Pie chart showing distribution of typhoid cases in Japan.]

Typhoid cases in USA

![Bar chart showing typhoid cases in USA from 2007 to 2010.]

- 2010: 439
- 2009: 347
- 2008: 439
- 2007: 413
IT CAN NOT BE FOOLED BY SAYING - THESE ARE NOT THE POPULATIONS YOU ARE LOOKING FOR!
**Typhoid Through the Centuries**

**Developing Countries**
- Municipal Water Treatment / Sanitation
- Urbanization

**Developed Countries**
- Enteric Fever Cases
- Municipal Water Treatment / Sanitation
- Urbanization

**Industrialization**

- 1800
  - Isolation of *S. typhi* organism (1880)
- 1850
  - Widal Diagnostic (1896)
- 1900
  - Development of heat-inactivated phenol-preserved whole-cell typhoid vaccine
  - Typhoid immunization available
- 1950
  - Chloramphenicol (1948+)
  - Acetone-inactivated whole-cell typhoid vaccine (1960s)
- 2000
  - Ty21a (live oral)
  - Purified Vi PS
- 2050
  - Quinolones and 3rd gen. cephalosporins
- 2100

**150 years**

- 1800-1950
- 1950-2000

**Legend**

- **Typhoid иммунизация**
- **Quinolones and 3rd gen. cephalosporins**
- **?? Vi conjugate??**
- **?? Single-dose live oral??**

**CHRF**

- Child Health Research Foundation
- Prevent Infections, Save Lives
How Big a Problem Is This and Where?

- Estimates 17-21.6 million cases
- 216,000 to 600,000 deaths
  - Comparable to many other diseases!
- Where?

Legend:
- High (>100 cases per 100,000 per year)
- Medium (10 – 100 cases per 100,000 per year)
- Low (<10 cases per 100,000 per year)
Typhoid Remains Neglected

• None at WHO
• No GAVI Initiative,
• Recent initiative from BMGF – DOMI (Diseases of the most impoverished) programme
• More Recently “Coalition Against Typhoid”
DOMI TYPHOID PROGRAM
Population-based studies

CHINA, INDIA, INDONESIA, PAKISTAN, VIETNAM

<table>
<thead>
<tr>
<th>Country</th>
<th>2-4Y</th>
<th>5-15Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakistan (Karachi)</td>
<td>573</td>
<td>413</td>
</tr>
<tr>
<td>India (Kolkata)</td>
<td>494</td>
<td>340</td>
</tr>
<tr>
<td>Indonesia (Jakarta)</td>
<td>180</td>
<td>149</td>
</tr>
<tr>
<td>Hue (Vietnam)</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Hechi (China)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
I HOPE THESE INITIATIVES COULD BE WITH BROADER PERSPECTIVES!
Bangladesh Team

TAKEN THEIR VISION OUT OF THE TUNNEL TO UNDERSTAND TYPHOID