Progress in typhoid epidemiology

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Overview

• Mode of transmission and sources
  – Evidence and importance

• Burden of disease
  – Current estimates and trends
  – Extrapolation, uncertainty, and data gaps
  – Severe disease and death
  – Occurrence by age
Modes of transmission

Direct transmission
- Direct contact
- Droplet spread

= ‘Person-to-person transmission’
Direct contact between persons without intermediaries

Indirect transmission
- Airborne
- Vectorborne
- Vehicleborne
Chain of infection

- Reservoir
- Portal of exit
- Source
- Mode of transmission
- Portal of entry
- Susceptible host

What is the source and predominant mode(s) of transmission?

What is the relative contribution of acute shedders versus chronic carriers?

Other
Mode of transmission in aggregate

• Mogasale systematic review and meta-analysis association between unimproved water and typhoid fever
  – Persons with unimproved water have 2.4 times odds of typhoid fever compared with those with improved water
  – Aggregating empiric studies is informative

• WHO Foodborne Diseases Epidemiology Reference Group Source Attribution Task Force, structured expert elicitation using Cooke's Classical Method
  – Water: 0.33-0.57
  – Food: 0.08-0.49
  – Other: 0.11-0.47

Mode of transmission locally

• **Foodborne**
  – Restaurant-associated outbreaks linked to chronic carriage in food handler in countries where typhoid is rare e.g., Colorado, United States

• **Waterborne**
  – Municipal water supplies e.g., Kathmandu, Nepal

• **Waterborne and foodborne**
  – Consuming surface water and produce grown in pit latrine seepage e.g., Central Division, Fiji
Role of infection class on transmission

• Fecal shedding classes following onset of acute illness
  – Acute shedding: <3 months
  – Convalescent carriers: ≥3-12 months
  – Chronic carriers: >12 months

• Things that we ‘know’
  – At low force of infection a larger proportion of acute typhoid is in age groups more susceptible to becoming chronic carriers
  – As acute typhoid infections approach zero the role of chronic carriers as the reservoir approaches 100%
  – Much to learn
## History of published estimates of typhoid burden

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<td><strong>Origin</strong></td>
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<td><strong>Coverage</strong></td>
<td>Global, except China</td>
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<td>Global</td>
<td>LMIC, unadjusted</td>
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<td>Global</td>
<td>Global, including paratyphoid</td>
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<tr>
<td>Illnesses (millions)</td>
<td>12.5</td>
<td>16.0</td>
<td>21.7</td>
<td>20.6</td>
<td>26.9</td>
<td>20.1</td>
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<td>11.0</td>
<td>12.5</td>
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<td>DALYs (thousands)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10,292</td>
<td>12,239</td>
<td>11,128</td>
<td>10,576</td>
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<tr>
<td>Deaths</td>
<td>600,000</td>
<td>216,510</td>
<td>223,000</td>
<td>-</td>
<td>144,890</td>
<td>190,200</td>
<td>160,700</td>
<td>148,800</td>
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</table>
Global population, 1980-2015
Global population and typhoid illness estimates
1980-2015

Excluded China
Global population and typhoid illness estimates
1995-2015

Population (billions)

Typhoid illnesses (millions)

Year
Typhoid incidence and deaths
1995-2015

Typhoid incidence/100,000/year

Year

Typhoid deaths per year
Extrapolation, uncertainty, and data gaps

• Improvements in methods for extrapolation

• Estimating uncertainty

• Data gaps
  – Areas and age groups needing incidence data
  – More and better data on disability and death
  – The ‘hidden’ problem in Oceania

Change in improved drinking water coverage by region, 1990 to 2015

Sub-Saharan Africa

Oceania

UNICEF and WHO. 2015
Typhoid fever in infants and young children aged <2 years

![Graph showing incidence per 100,000/year vs. age (months)].

- **Protection, disease, and lack of exposure**
- **Underascertainment by blood culture**
- **Underuse**
  - Maternal antibody
  - Breastfeeding
- **Volume inadequacy**
- **Contamination**

**Force of infection**
William Budd, b. 14 Sep 1811, d. 9 Jan 1880
Role of infection class in transmission

- Things that we would like to know more about
  - Proportion stool cultures positive in acute disease vs. chronic carriage
  - Concentration of *Salmonella* Typhi in feces in acute disease vs. chronic carriage

Thomson S. J Hyg 1954; 52: 67-70
Distribution of typhoid fever by age group at various incidence levels, 2000

Typhoid fever DALYs and deaths by age
Global Burden of Disease 2015

Disability Adjusted Life Years

Deaths

http://vizhub.healthdata.org/gbd-compare/
Social inequity

- **High-income countries**
  - Declined following increased access to safe water and food in urban areas
  - Disease of travelers, beneficiaries of typhoid vaccines

- **Low- and middle-income countries**
  - Poor sanitation, unsafe water and food
  - Crowding
  - Limited access to vaccines
Acute disease and chronic carriage as reservoir

Proportion of infections with chronic carrier as reservoir

Typhoid incidence level

None
Low
Medium
High
Very high
Deaths by cause and age, Hamburg, Germany, 1872-1900

Typhoid fever deaths

Infant deaths

Elbe River water filtered

1872 1900

Improved drinking water coverage, global, 2015

UNICEF and WHO. 2015
Data inequity

- **High-income countries**
  - Laboratory confirmation
  - Notifiable disease with high reporting
  - Robust data

- **Low- and middle-income countries**
  - Dependence on clinical diagnosis
  - Weak surveillance with low reporting
  - Poor quality routine data
  - Special studies
Moving targets for vaccine

• Person, place, and time
  – Vaccination of ‘high risk groups and populations’ based on ‘local epidemiologic situation’
  – Who should be vaccinated and where?

• Age
  – ‘Immunization of school-age and/or preschool-age children’
  – Typhoid conjugate vaccines can protect below 2 years of age
  – At what age should we vaccinate to prevent the most disease?
Global distribution of typhoid fever, 2000 vs. 2010

Salmonella enterica bloodstream infections, Queen Elizabeth Central Hospital, Blantyre, Malawi, 1998-2014

Conclusions

• Current typhoid fever estimates are remarkably consistent, improving with
  – New data
  – Better extrapolation and modeling

• Data are weakest in areas with most disease
  – Complications and death

• Typhoid fever incidence varies in person, place, and time
  – Targeting vaccine is challenging
  – Need to understand more about disease in infants and young children
Role of infection class in transmission

- Fecal shedding classes following onset of acute illness
  - Acute shedding: <3 months
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  - Chronic carriers: >12 months

- Things that we ‘know’
  - At low force of infection a larger proportion of acute typhoid is in age groups more susceptible to becoming chronic carriers
  - As acute typhoid infections approach zero the role of chronic carriers as the reservoir approaches 100%
Role of infection class in transmission

• Things that we would like to know more about
  – Proportion stool cultures positive higher in acute disease vs. chronic carriage?
  – Concentration of *Salmonella* Typhi in feces higher in acute disease vs. chronic carriage?
    • Chronic carriers (when positive): $10^6$-$10^{10}$ CFU/g (Merselis)
    • $<10^2$-$10^7$ (Thomson)