Typhoid Fever in Santiago, Chile: Modern Insights Where Historical Data Meet Mathematical Modeling

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Outline

• Santiago overview
• Modeling project
• Model fitting
• Take-aways: site specific and new locations
• Understanding uncertainty in the face of vaccine projections
Santiago, Chile

- Very low level typhoid incidence in modern day
- In the 1970-1980s: high endemic transmission despite >90% drinking water coverage and 80% connection to sewer system
- Decline in 1980s coincident with Ty21a vaccine trial, carrier finding and treatment
- 1991 ban of wastewater irrigation: sharp decline in cases
Santiago, Chile

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Why model in Santiago?

• Three different transmission periods in a single population/demographic set
• Data that is not commonly available:
  – Age distribution, seasonality, *transmission route*, *carrier prevalence*, *short cycle-only transmission*
• Allows us to explore underlying mechanisms for observed dynamics and understand areas of uncertainty
Modeling approach

Individual-based model:
• Allows for *individual level* variation in parameters including immunity, shedding duration, and carrier probabilities
Modeling approach

Key components:
- Infections can be either *acute* or *subclinical*
- Permanent chronic carrier state
- Protection-per-infection parameter
Modeling transmission routes

Distinct transmission routes in model:

**Long cycle**: Homogenous mixing, dose-response dynamics, decay in water/environment

**Short cycle**: Non-seasonal, modeled as direct transmission
Model fitting process

- Optimization to maximize likelihoods informing model fit to age distribution, incidence, carrier prevalence, seasonality
- Provides point estimates for fitted parameters
Take-aways from model fitting

*Immunity* likely drives low incidence in adults

- Partial immunity after infection creates adult age distribution

We are likely catching a small fraction of total cases:

- <10% total cases (clinical/subclinical) reported in model

Pre-vaccine age distribution of typhoid incidence in Santiago, Chile
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![Graph showing pre-vaccine age distribution of typhoid incidence in Santiago, Chile](image.png)
Take-aways from model fitting

*Exposure* likely drives childhood age distribution:
- Increases in incidence correlated with entry ages into preschool, elementary school system → potential exposure to new foods
Take-aways from model fitting

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![Graph showing Under 20 age distribution of typhoid incidence in Area Norte](image-url)
Under 20 age distribution of typhoid incidence in Area Norte

**Exposure** likely drives childhood age distribution:

- Increases in incidence correlated with entry ages into preschool, elementary school system → potential exposure to new foods

Take-aways from model fitting
We can estimate the probability of becoming a chronic carrier from infection

- Age/gender distribution determined by age distribution of gallstones
- Point estimates of probability of becoming a chronic carrier in range of estimates from Ames, 1943

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>20-29</td>
<td>0.68</td>
<td>3.3</td>
</tr>
<tr>
<td>30-39</td>
<td>2.0</td>
<td>6.0</td>
</tr>
<tr>
<td>40-49</td>
<td>2.5</td>
<td>7.2</td>
</tr>
<tr>
<td>50-59</td>
<td>3.0</td>
<td>8.4</td>
</tr>
<tr>
<td>60-69</td>
<td>3.7</td>
<td>9.7</td>
</tr>
<tr>
<td>70-79</td>
<td>6.5</td>
<td>9.7</td>
</tr>
<tr>
<td>80-90</td>
<td>6</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Best-fit model estimates, cases resulting in carriers (%)

- Prevalence of chronic carriers
- Point estimates of probability of becoming a chronic carrier in range of estimates from Ames, 1943
Impact of carriers in Santiago

- Acute transmission, chronic carriers both can trade-off to contribute to short cycle transmission in endemic period
Impact of carriers in Santiago

• Acute transmission, chronic carriers both can trade-off to contribute to short cycle transmission in endemic period
• Extra data point: allows us to better estimate chronic carriage vs. acute transmission
Multiple fits to Santiago data are possible within parameter uncertainty

**Daily exposure rate: 0.5**
Approximately 50% of population exposed daily

**Daily exposure rate: 0.005**
Approximately 0.5% of population exposed daily

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Source: QMRA wiki

Seasonality

Age Distribution

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Simulation

Data
Multiple fits to Santiago data are possible within parameter uncertainty

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Seasonality

**Age Distribution**

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**Age Distribution**
History matching for unknown parameters

- Many parameter combinations can be fitted to data
- Automated methods to find best fit points across range of parameter unknowns
- Estimate error bounds due to parameter uncertainty for WASH/ vaccine intervention projections
Perspectives from modeling historical data

• Many model mechanisms for Santiago can be used in modern locations

• Age specific exposure, seasonality, need to be understood from site to site: data available?

• Even with many variables that are typically unknown in most settings (transmission route, chronic carriers burden and impact), we still have parameter unknowns that would affect uncertainty estimates for vaccination

• New tools will provide built-in error-bound estimates for vaccine impact due to parameter uncertainty
Thank you!

Santiago data sharing:
• Catterina Ferreccio
• Rosanna Lagos

jgauld@intven.com
**Salmonella Typhi & S. Paratyphi isolates from pediatric enteric fever cases, Area Norte, Santiago, 2006-2015**

<table>
<thead>
<tr>
<th>Year</th>
<th>Casos &lt;15 years</th>
<th>Annual mean population, age &lt;15 yrs</th>
<th>Annual mean Typhi incidence, age &lt;15 yrs/10^5</th>
<th>Annual mean Paratyphi B incidence, age &lt;15 yrs/10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td>56*</td>
<td>27,305</td>
<td>227.1</td>
<td></td>
</tr>
<tr>
<td>2006-10</td>
<td>12</td>
<td>185,930</td>
<td>0.64</td>
<td>0.32</td>
</tr>
<tr>
<td>2011-15</td>
<td>5</td>
<td>194,873</td>
<td>0.25</td>
<td>0</td>
</tr>
</tbody>
</table>

* This group included children from 6-17 years of age who received placebo enrolled in a field trial in Area Norte.

The 18 cases of enteric fever in years 2006-2010 was higher than the 5 cases in years 2011-2015 (p=0.0089, corrected Chi square)