Invasive non-typhoidal *Salmonella* in Asia: An emerging infection?

Stephen Baker 01/02/13
Species and subspecies were originally defined by DNA-DNA hybridisation, confirmed by MLEE and MLST and are currently differentiated by biochemistry and serology.

The split in typhoidal and non-typhoidal is based on the disease syndrome. Typhoid and paratyphoid fever is prolonged, whilst extra-intestinal infection is usually acute and metastatic. Gastroenteritis is characterised by diarrhoea.

Differentiation of serovars is by agglutination with specific antisera against LPS (O), two phases of flagella (H1 and H2). There are 46 O, 85 H and 1 capsule (Vi) antigen which have been described in about 1,500 combinations within subspecies I.
Salmonella Epidemiology

• Estimated 93.8 million cases of gastroenteritis due to *Salmonella spp* with 155,000 deaths occur globally each year (Majowicz et al, CID, 2010).

**In developed countries**

• Report from US: estimated 1.4 million infections (population 293 million) with 168,000 visits to GP (Mead PS et al, 1999)

• Report from UK: 41,000 cases occur each year (population 60 million, resulting in 1,500 hospitalization and 119 deaths. (McDermott, 2006)

**In developing countries**

• Report from Africa: NTS is the most common cause of bacteremia in sub Saharan Africa, results in 1 million cases/year, case fatality rate around 20% (Crump JA, Lancet Infect. Dis., 2010)
Enteric infections where I am

NT *Salmonella*
The decline of typhoid and the rise of non-typhoid salmonellae and fungal infections in a changing HIV landscape: bloodstream infection trends over 15 years in southern Vietnam

How does our invasive NTS relate to that seen in Africa?

- **Fever**: 95% of cases, no apparent focus in 35%
- **Pneumonia**: 60% of children and 30% of adults have an apparent lower respiratory tract infection focus, commonly due to co-infection
- **Diarrhoea**: 20–50% of cases, but often not a prominent feature
- **Blood tests**: Severe anaemia in 40–50% of adults and 25–40% of children, 95% of adults and 20% of children are HIV positive, CD4 count <200 cells per μL in 80% of adults
- **Splenomegaly**: 30–45% of cases
- **Hepatomegaly**: 15–35% of cases
Case/control for gastrointestinal NTS infections

- May 2009-December 2010
- 1,419 total cases under 5 years of age
- 77 (5.4%) were infected with *Salmonella*

- 609 total controls
- 38 (6.2%) of the controls were infected with *Salmonella* but were asymptomatic
Descriptive characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Salmonella (n=77)</th>
<th>All cases (n=1342)</th>
<th>Controls (n=571)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>63.6</td>
<td>63.8</td>
<td>63.2</td>
</tr>
<tr>
<td>Breastfed, %</td>
<td>77.9</td>
<td>71.3</td>
<td>77.6</td>
</tr>
<tr>
<td>Median age (IQR)*</td>
<td>10 (6.5-15)</td>
<td>13 (8-20)</td>
<td>12 (8-21)</td>
</tr>
<tr>
<td>Median z-score (IQR)</td>
<td>-0.3 (-1 to 0.5)</td>
<td>-0.3 (-0.8 to 0.6)</td>
<td>-0.8 (-1 to -0.2)</td>
</tr>
</tbody>
</table>

* months
Seasonality

The graph illustrates the percentage of total presenting patients with a focus on Salmonella infections and the average temperature in °C for each month from January to December. The percentage of patients increases significantly in May and June, peaks in July, and then decreases steadily until December.
**Univariate & multivariate analyses**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
<th>AOR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous illness</td>
<td>2.21</td>
<td>1.08-4.52</td>
<td>0.029*</td>
<td>1.77</td>
<td>0.73-4.26</td>
<td>0.204</td>
</tr>
<tr>
<td>Symptomatic contact</td>
<td>3.14</td>
<td>1.12-8.83</td>
<td>0.030*</td>
<td>5.98</td>
<td>1.76-20.36</td>
<td>0.004*</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.96-1.00</td>
<td>0.036*</td>
<td>0.97</td>
<td>0.94-0.99</td>
<td>0.021*</td>
</tr>
<tr>
<td>Hand washing</td>
<td>2.67</td>
<td>1.29-5.53</td>
<td>0.008*</td>
<td>1.99</td>
<td>0.85-4.63</td>
<td>0.111</td>
</tr>
<tr>
<td>Market food</td>
<td>2.22</td>
<td>1.27-3.88</td>
<td>0.005*</td>
<td>2.27</td>
<td>1.22-4.24</td>
<td>0.010*</td>
</tr>
<tr>
<td>&gt;2 children in house</td>
<td>2.32</td>
<td>1.26-4.29</td>
<td>0.007*</td>
<td>2.32</td>
<td>1.15-4.67</td>
<td>0.019*</td>
</tr>
<tr>
<td><em>Outside toilet</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1.67</td>
<td>0.41-6.81</td>
<td>0.475</td>
<td>1.53</td>
<td>0.30-7.86</td>
<td>0.612</td>
</tr>
<tr>
<td>Urban</td>
<td>0.27</td>
<td>0.11-0.70</td>
<td>0.007*</td>
<td>0.25</td>
<td>0.09-0.72</td>
<td>0.010*</td>
</tr>
</tbody>
</table>

OR: Odds ratio; CI: Confidence interval; AOR: Adjusted Odds Ratio
*p-value ≤0.05
^Answering “No” or “Don’t Know” to the question “Does the child wash their hands after using the toilet?”
<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Cases (N=79)</th>
<th>Asymptomatic (N=95)</th>
<th>Total (N=174)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derby</td>
<td>2</td>
<td>2.5</td>
<td>7</td>
<td>7.4</td>
</tr>
<tr>
<td>Paratyphi B mono</td>
<td>2</td>
<td>2.5</td>
<td>2</td>
<td>2.1</td>
</tr>
<tr>
<td>Stanley</td>
<td>4</td>
<td>5.1</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Typhimurium</td>
<td>34</td>
<td>43.0</td>
<td>8</td>
<td>8.4</td>
</tr>
<tr>
<td><strong>Group C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newport</td>
<td>3</td>
<td>3.8</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Group D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteritidis</td>
<td>1</td>
<td>1.3</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>No group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weltevreden</td>
<td>9</td>
<td>11.4</td>
<td>24</td>
<td>25.3</td>
</tr>
</tbody>
</table>

*p ≤ 0.05
Animal contact as a source of human NTS infection

• Potential route human to human transmission

• Why?
  - African studies: Same NTS serovars was obtained from contacts and index cases, but not from animals and environment in Kenya (Kariuki S et al, JCM, 2006)
  - Clonal differences between NTS recovered from children and animals living in close contact in The Gambia (Dione M et al, Plos Neglected Tropical Disease, 2011)

• Our risk factors of NTS gastrointestinal infection in children under 5 years old
  - "Salmonella patients were more likely to report a recent diarrhoeal contact, to live in a household with >2 children" (Thompson C et al, Epidemiol. Infect, 2012)

Central dogma of *Salmonella* transmission
13 stool (65%)
3 carriage (15%)
4 blood (20%)

17 stool (29%)
2 carriage (0.03%)
30 blood (51%)
Ongoing and future work

Animal sampling for *Salmonella*
- Pigs, chickens, ducks, reptiles, shellfish

**MLST**
- 500+ isolates from different hosts
- That asymptomatic strains have an animal reservoir
- Invasive strains are transmitted from human to human (or a secondary reservoir)

**Retrospective analysis of invasive NTS**
- Outcome, risk factors for outcome, disease history, HIV rate
- Low morality rate, weak effect of HIV, liver abnormalities are common

**Case/control investigation for invasive NTS**
- Currently in design

**1000 child cohort**
- To assess Salmonella incidence in the first 3 years of life
- Assess long term carriage of NTS serotypes
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