Understanding transmission of invasive non-typhoidal *Salmonella*

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**Salmonella** taxonomy

<table>
<thead>
<tr>
<th>Species</th>
<th>S. <em>enterica</em></th>
<th>S. <em>bongori</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subspecies</strong></td>
<td>enterica (I)</td>
<td>salamae (II)</td>
</tr>
<tr>
<td></td>
<td>arizonae (IIIa)</td>
<td>diarizonae (IIIb)</td>
</tr>
<tr>
<td></td>
<td>houtenae (IV)</td>
<td>indica (VI)</td>
</tr>
</tbody>
</table>

| Usual habitat    | Warm blooded animals | Cold-blooded animals and environment |

- >2600 serovars
- New serovars emerging
- Well-described host-specificity, but some serovars may be promiscuous
# Predominant invasive serovars

<table>
<thead>
<tr>
<th>Serotype (invasive index)</th>
<th>USA, 1996-1999 (N=447)*</th>
<th>Australia/Canada/Denmark/Finland, 2000-2007 (N=177)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typhimurium (1.6)</strong></td>
<td>0.9 per 100,000/year</td>
<td>0.8 per 100,000/year</td>
</tr>
<tr>
<td>Enteritidis (1.8)</td>
<td>30%</td>
<td>11%</td>
</tr>
<tr>
<td>Heidelberg (7.0)</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Dublin (33.3)</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Choleraesuis (55.2)</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>Schwarzengrund (10.8)</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>Newport (2.6)</td>
<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>Virchow (4.4)</td>
<td>-</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Vugia, 2004; **Laupland, 2010; ††Langridge 2009
Mechanisms – 1

*Salmonella* and host adaptation

- Interaction with host through host-specific invasion: attachment, escape IR, survival in host macrophages & dendritic cells.
- Common core of virulence genes.
- *Salmonella* Pathogenicity Islands: genes encoding proteins responsible for host IR & virulence factors exploiting host processes.
- SPI1 -SPI5 common to all serovars.
- ~23 SPIs described.
Mechanisms (2)

- Person-to-person, including nosocomial disease – adaptation of “non-human serotypes” as human pathogens
  - *Salmonella* Typhimurium ST313 (Okoro et al; 2012)
  - New evidence that *Salmonella* Enteritidis has also become host adapted.
  - *Salmonella* Isangi – documented nosocomial outbreaks

Snapshot of dendrogram to illustrate PFGE banding patterns in invasive *Salmonella* Isangi isolates South Africa
Mechanisms (3)

- Environmental contamination – related to human-to-human transmission as well as foodborne disease:
  - Kenyan data suggest that in Africa different pathotypes circulate among humans versus domesticated animals: some environmental contamination (Kariuki et al; 2006).
  - Contamination of hospital environment in nosocomial transmission (Smith et al; 2014).
Foodborne disease – how host specific is this

• Reports of invasive *Salmonella* Enteritidis and *Salmonella* Typhimurium associated with foodborne outbreaks; molecular similarity to food animal isolates, including chicken, beef, pork.

• *Salmonella* Dublin - beef and dairy products: raw milk; raw calves’ liver

• *Salmonella* Newport - cattle & horse meat.

• *Salmonella* Choleraesuis - pork: - localisation of disease in elderly.

• Rarer serotypes e.g. *Salmonella* Isangi – outbreak reports: pork, milk formula, chicken, eggs -
Predisposing factors for invasive disease

- Extremes of age – the very old and the very young; role of HIV-exposure in HIV uninfected infants.
- Immunosuppression – HIV; malignancy; immunosuppressive therapy.
- Malnutrition
- Malaria
- Sickle cell disease
- Schistosomiasis
Other considerations

• Malaria - interaction with cells infected by *Plasmodium*.
• Sickle cell disease and malaria – role of abnormal iron metabolism and functional asplenia.
• Sickle cell disease - osteomyelitis.
• Predilection for damaged tissue.
• Genetic predisposition to disease – related to age, sex, race?
• Cystic fibrosis – CFTR association in typhoid fever – iNTS equivalent?
Salmonella invasion

Invasive Salmonella serovar

SPI-1: Effector secretion

SipA, SipB, SopB, SopD, SopE, SopE2

Translocation across epithelial barrier

Intestinal epithelium

Cytokine secretion: IL-1, IL-8, TNFα

Basolateral invasion

Macrophage

Phagocytosis

Cytokine secretion: IL-1, IL-6, TNFα; IL-12, IL-8; IL-1β

Survival and proliferation

Basolateral reseeding of epithelial cells

Adapted from Hurley et al; 2014
Host Immunity

- Host-specific *Salmonella* serovars – adapted to overcoming immunity in that host only
- Capitalise on immature / malfunctioning immune systems: failure of “host-specific barrier” in preventing disease.
- Neonates and very young – failure of protective immunity from mother.

1. Loss of specific CD4+ cells
2. Cellular cytokine dysregulation
3. Humoral defects

Feasey *et al*; 2012
Nosocomial transmission

• Increased risk of invasion with MDR serotypes.
• At-risk patients: immune-suppressed.
• Host adaptation may favour certain serotypes or pathotypes – non-invasive outbreak in neonates in RSA (2012) due to *Salmonella* Typhimurium ST19.
Age-related incidence rates – invasive disease

*Vugia et al; 2004

**Laupland et al; 2010
Age-related incidence: Global Burden of iNTS

Ao et al, 2015 (EID in press)
Implications for control

• Need to understand where and why: food (including food animals); environment (including nosocomial); patient (immune suppression & genetics); population (vaccine campaigns etc).
• Need more evidence of host adaptation and how and where this occurs.
• Need more understanding of the immunology and the role of diseases besides HIV for management and prevention campaigns.
• Panel discussion: 3 May 2015
Thank you!

A Sooka
AM Smith
CED staff
GERMS-SA