Understanding transmission of invasive non-typhoidal *Salmonella*

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Salmonella taxonomy

Species	*S. enterica*						*S. bongori* (V)
Subspecies	*enterica* (I)	*salamae* (II)	*arizonae* (IIIa)	*diarizonae* (IIIb)	*houtenae* (IV)	*indica* (VI)	
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

	USA, 1996-1999 (N=447)*	Australia/Canada/ Denmark/Finland, 2000-2007 (N=177)**
Serotype (invasive index‡‡)	0.9 per 100,000/year	0.8 per 100,000/year
Typhimurium (1.6)	30%	11%
Enteritidis (1.8)	16%	20%
Heidelberg (7.0)	13%	12%
Dublin (33.3)	4%	4%
Choleraesuis (55.2)	3%	-
Schwarzengrund (10.8)	2%	-
Newport (2.6)	-	5%
Virchow (4.4)	-	4%

*Vugia, 2004; **Laupland, 2010; ‡‡Langridge 2009

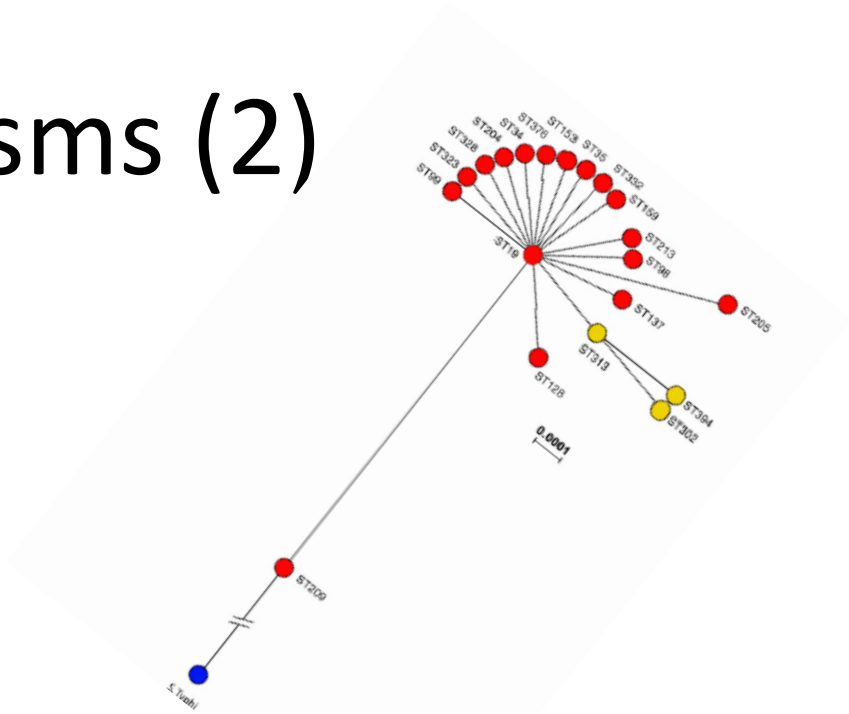
Mechanisms – 1

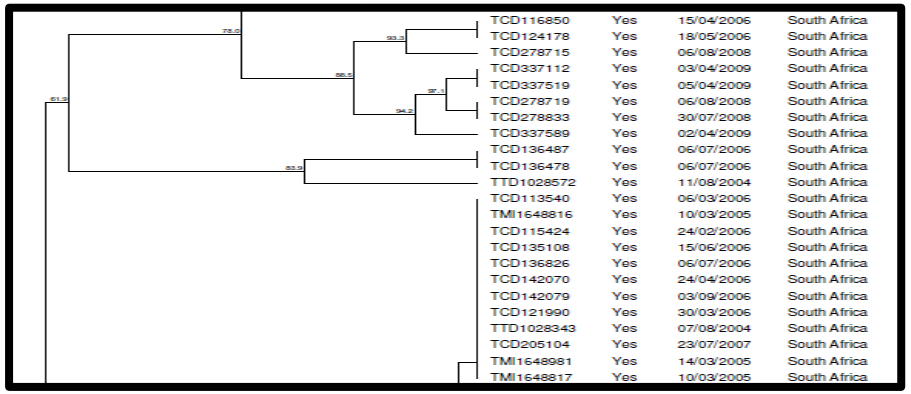
Salmonella and host adaptation

- 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





TCD116850	Yes	15/04/2006	South Africa
TCD124178	Yes	18/05/2006	South Africa
TCD278715	Yes	06/08/2008	South Africa
TCD337112	Yes	03/04/2009	South Africa
TCD337519	Yes	05/04/2009	South Africa
TCD278719	Yes	06/08/2008	South Africa
TCD278833	Yes	30/07/2008	South Africa
TCD337589	Yes	02/04/2009	South Africa
TCD136487	Yes	06/07/2006	South Africa
TCD136478	Yes	06/07/2006	South Africa
TTD1028572	Yes	11/08/2004	South Africa
TCD113540	Yes	06/03/2006	South Africa
TMI1648816	Yes	10/03/2005	South Africa
TCD115424	Yes	24/02/2006	South Africa
TCD135108	Yes	15/06/2006	South Africa
TCD136826	Yes	06/07/2006	South Africa
TCD142070	Yes	24/04/2006	South Africa
TCD142079	Yes	03/09/2006	South Africa
TCD121990	Yes	30/03/2006	South Africa
TTD1028343	Yes	07/08/2004	South Africa
TCD205104	Yes	23/07/2007	South Africa
TMI1648981	Yes	14/03/2005	South Africa
TMI1648817	Yes	10/03/2005	South Africa

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

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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*; 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 -

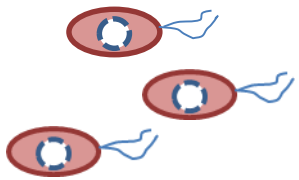
Predisposing factors for invasive disease

- 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

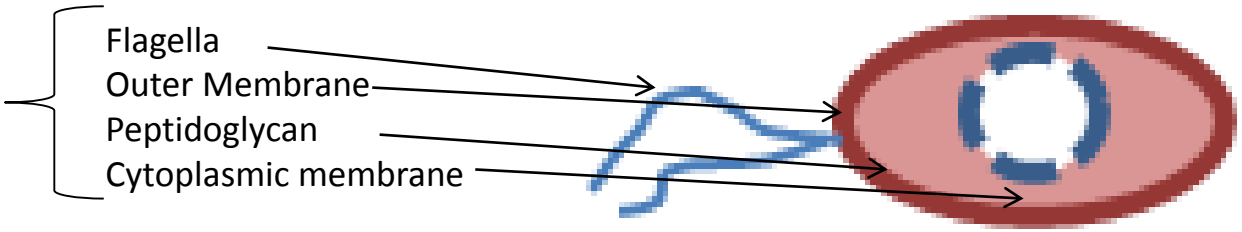
Other considerations

- 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



Translocation across epithelial barrier

SPI-1: Effector secretion

SipA, SipB, SopB, SopD, SopE, SopE2

Intestinal epithelium

M cell

Cytokine secretion: IL-1,IL-8, TNFα

Basolateral invasion

Basolateral reseeding of epithelial cells

Macrophage

Phagocytosis

Survival and proliferation

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

Adapted from Hurley *et al*; 2014

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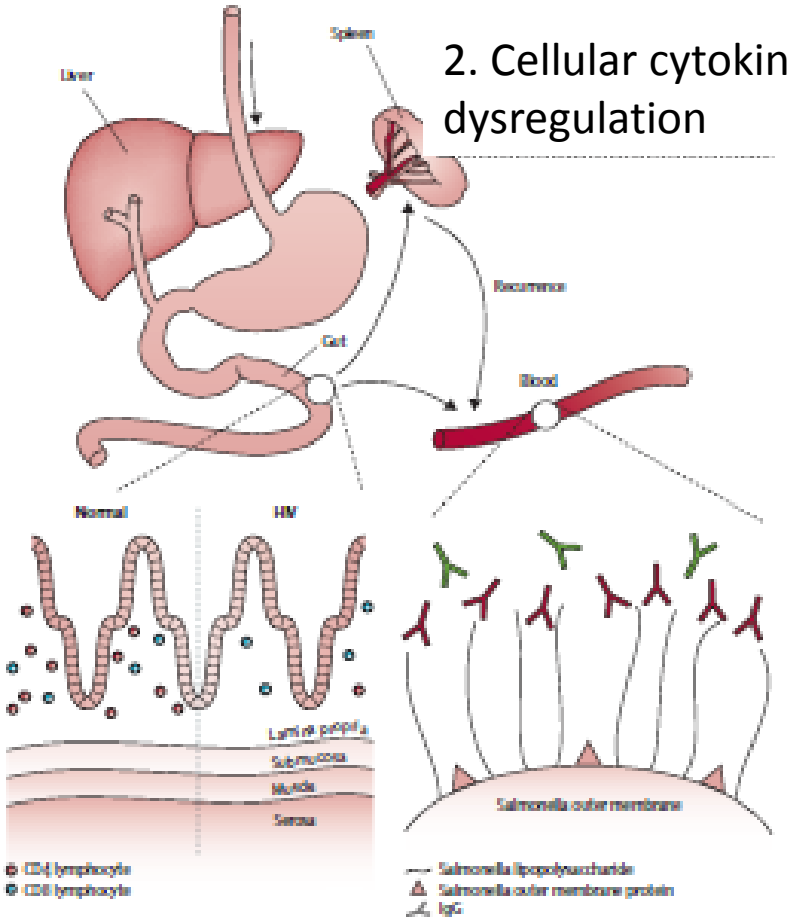
Host Immunity

- 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.



2. Cellular cytokine dysregulation

1. Loss of specific CD4+cells

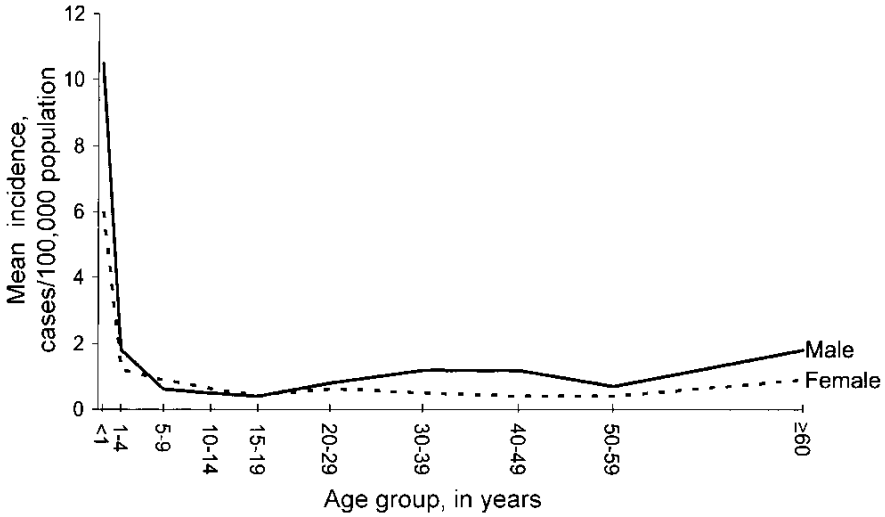
3. Humoral defects

Feasey *et al*; 2012

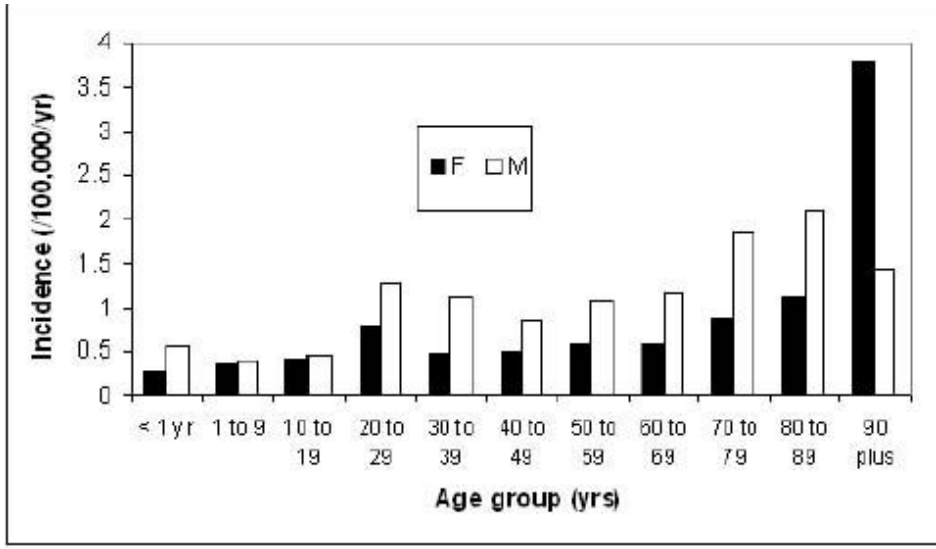
Nosocomial transmission

- Numerous literature reports of nosocomial transmission, including *Salmonella* Typhimurium, *Salmonella* Enteritidis, *Salmonella* Schwarzengrund, *Salmonell*a Isangi.
- 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

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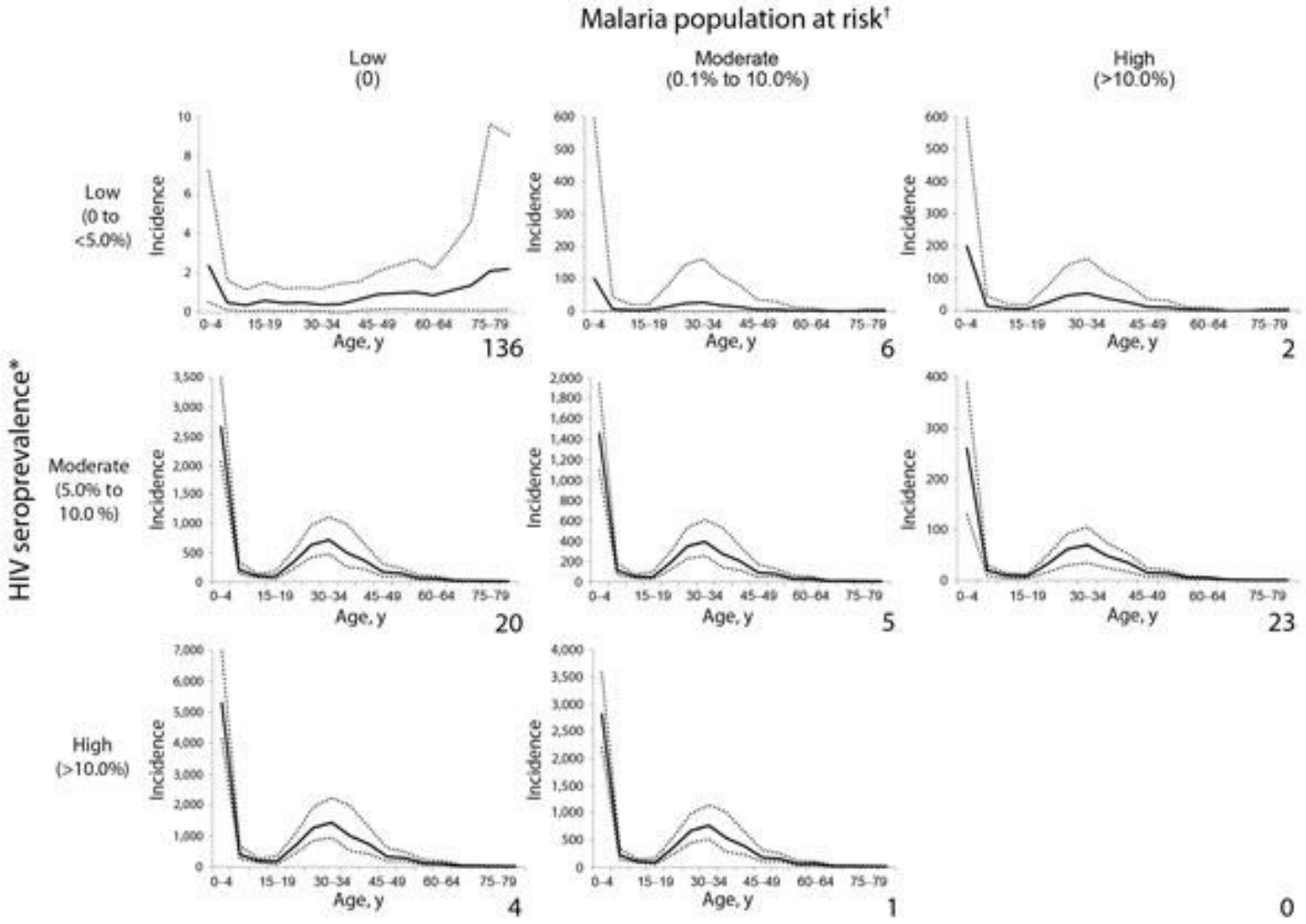
Age-related incidence: Global Burden of iNTS



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!

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GERMS-SA

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