

# Understanding transmission of invasive non-typhoidal *Salmonella*

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# Salmonella taxonomy

Species	<i>S. enterica</i>					<i>S. bongori</i> (V)
Subspecies	<i>enterica</i> (I)	<i>salamae</i> (II)	<i>arizonae</i> (IIIa)	<i>diarizonae</i> (IIIb)	<i>houtenae</i> (IV)	<i>indica</i> (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)**	South Africa, 2003-2013 (N=8462)‡	South Africa, Animal data 2013-02/2015 (N=8663)‡
Serotype (invasive index <sup>‡‡</sup> )	0.9 per 100,000/year	0.8 per 100,000/year	1.6 per 100,000/year (1.2 – 2.0)	
<b>Typhimurium (1.6)</b>	<b>30%</b>	<b>11%</b>	<b>46%</b>	<b>4%</b>
<b>Enteritidis (1.8)</b>	<b>16%</b>	<b>20%</b>	<b>24%</b>	<b>19%</b>
<b>Heidelberg (7.0)</b>	<b>13%</b>	<b>12%</b>	<b>1%</b>	<b>1%</b>
<b>Dublin (33.3)</b>	<b>4%</b>	<b>4%</b>	<b>4%</b>	-
<b>Choleraesuis (55.2)</b>	<b>3%</b>	-	<b>&lt;1%</b>	-
<b>Schwarzengrund (10.8)</b>	<b>2%</b>	-	<b>&lt;1%</b>	<b>3.1%</b>
<b>Newport (2.6)</b>	-	<b>5%</b>	<b>&lt;1%</b>	<b>&lt;1%</b>
<b>Virchow (4.4)</b>	-	<b>4%</b>	<b>1%</b>	<b>&lt;1%</b>

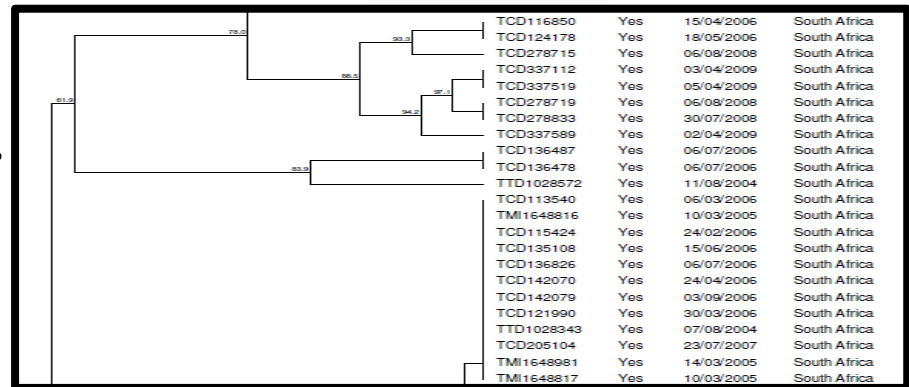
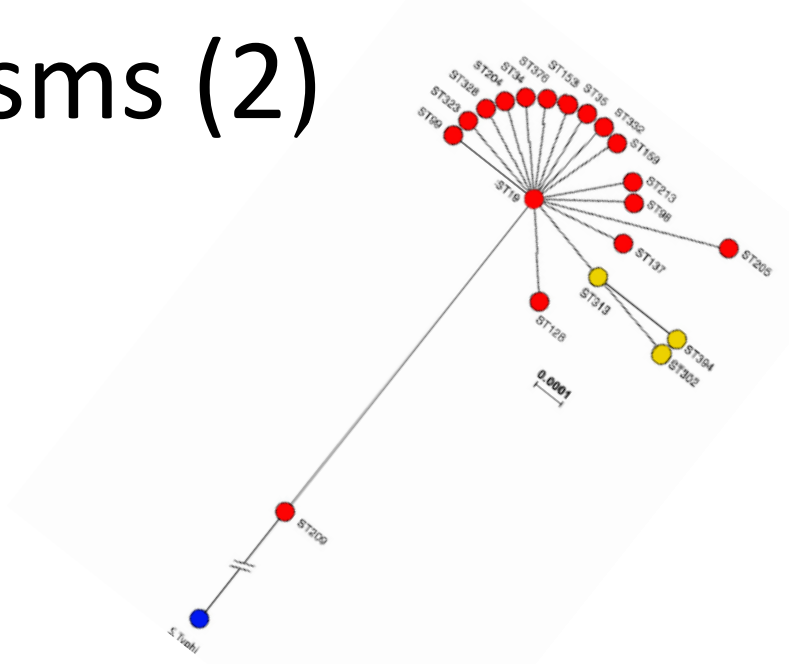
# Mechanisms – 1

## *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*; 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 -

Protein shakes widely used in RSA for AIDS patients  
pre-HAART?

# Predisposing factors for invasive disease

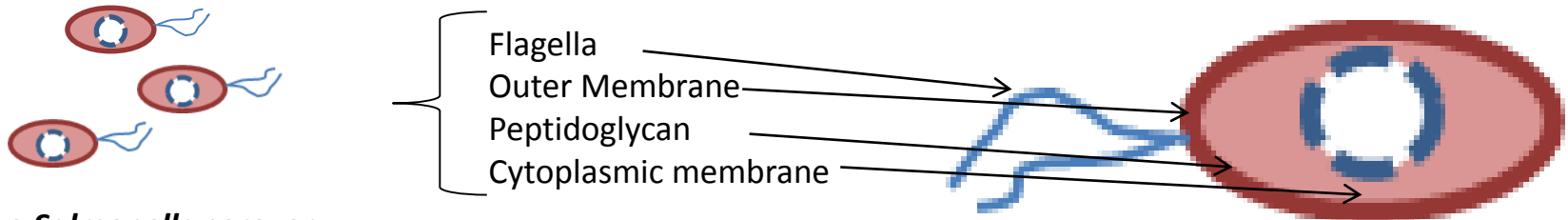
- Extremes of age – the very old and the very young; role of HIV-exposure in HIV uninfected infants.
- Immunosuppression – HIV; malignancy; immunosuppressive therapy.
- Malnutrition
- Malaria
- Sickle cell disease
- Schistosomiasis



# 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



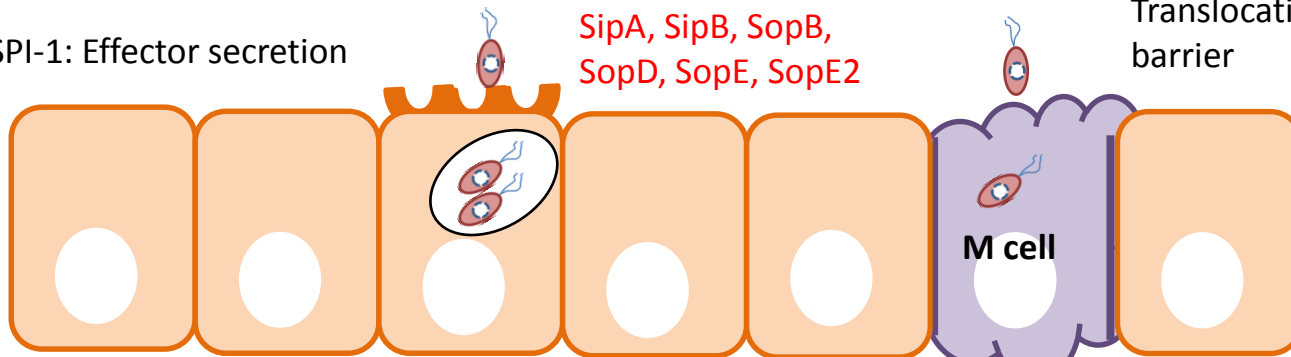
Invasive *Salmonella* serovar

SPI-1: Effector secretion

SipA, SipB, SopB,  
SopD, SopE, SopE2

Translocation across epithelial barrier

Intestinal epithelium

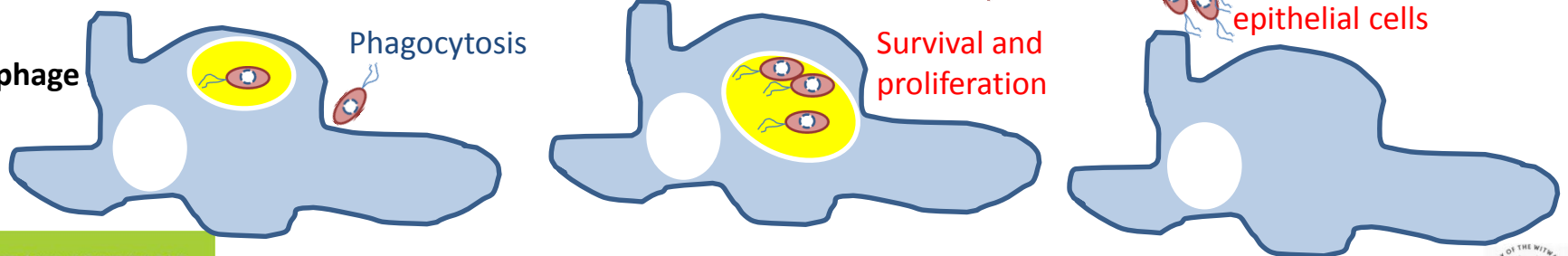


Cytokine secretion: IL-1, IL-8, TNF $\alpha$

Basolateral invasion

Basolateral reseeding of epithelial cells

Macrophage

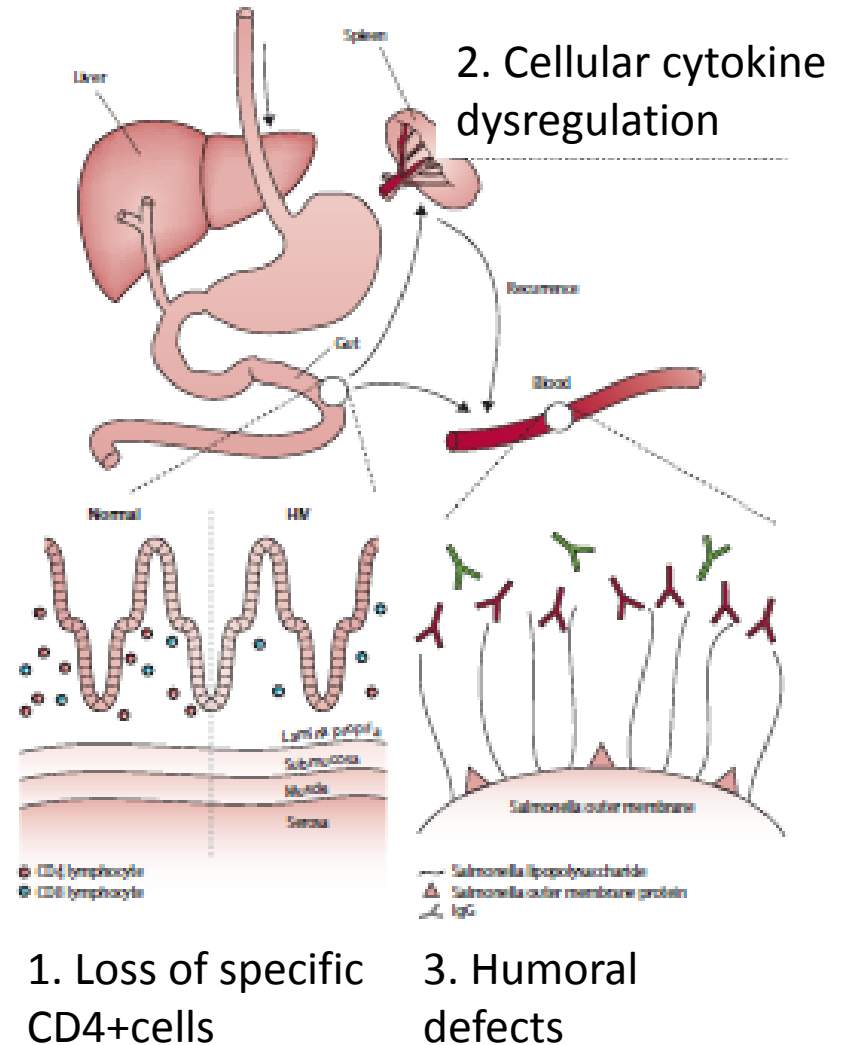


Cytokine secretion: IL-1, IL-6 TNF $\alpha$ ; IL-12, IL-8; IL-1 $\beta$

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.

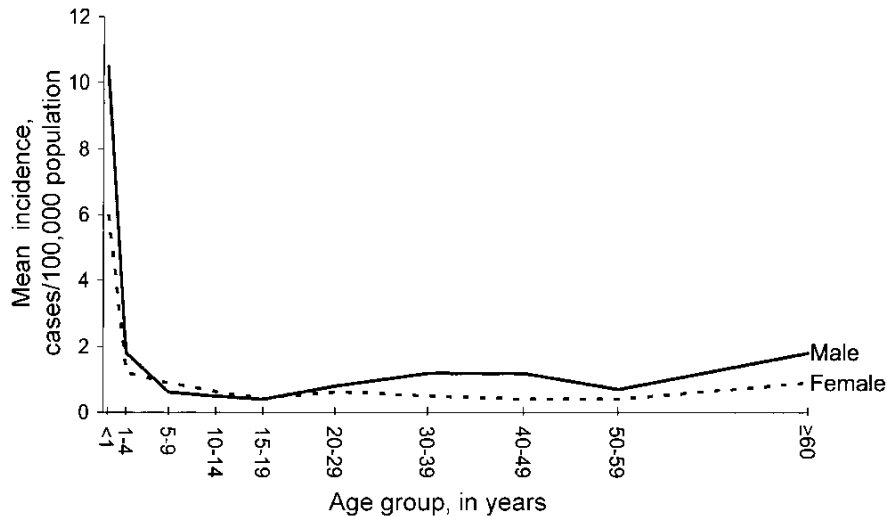


Feasey *et al*; 2012

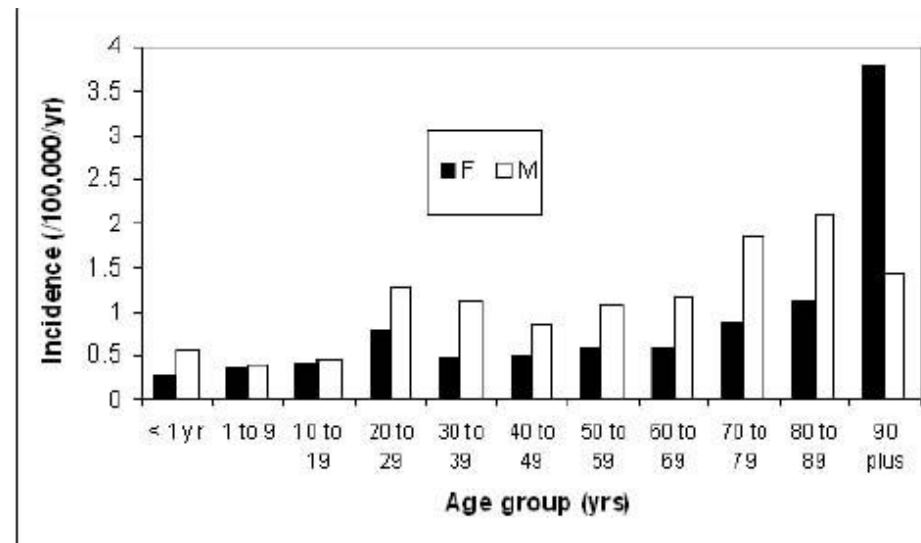
# Nosocomial transmission

- Numerous literature reports of nosocomial transmission, including *Salmonella* Typhimurium, *Salmonella* Enteritidis, *Salmonella* Schwarzengrund, *Salmonella* 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

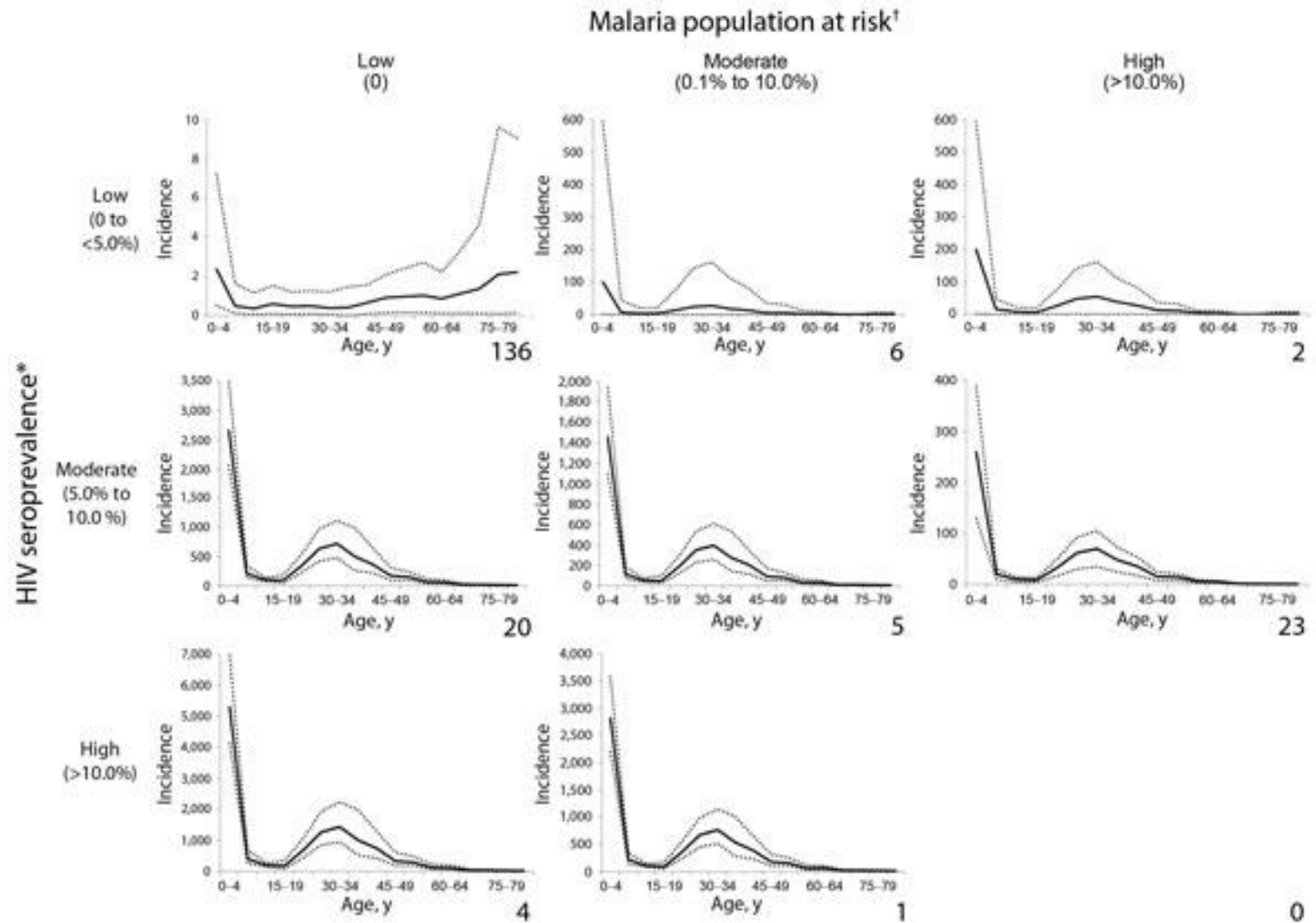


\*Vugia *et al*; 2004



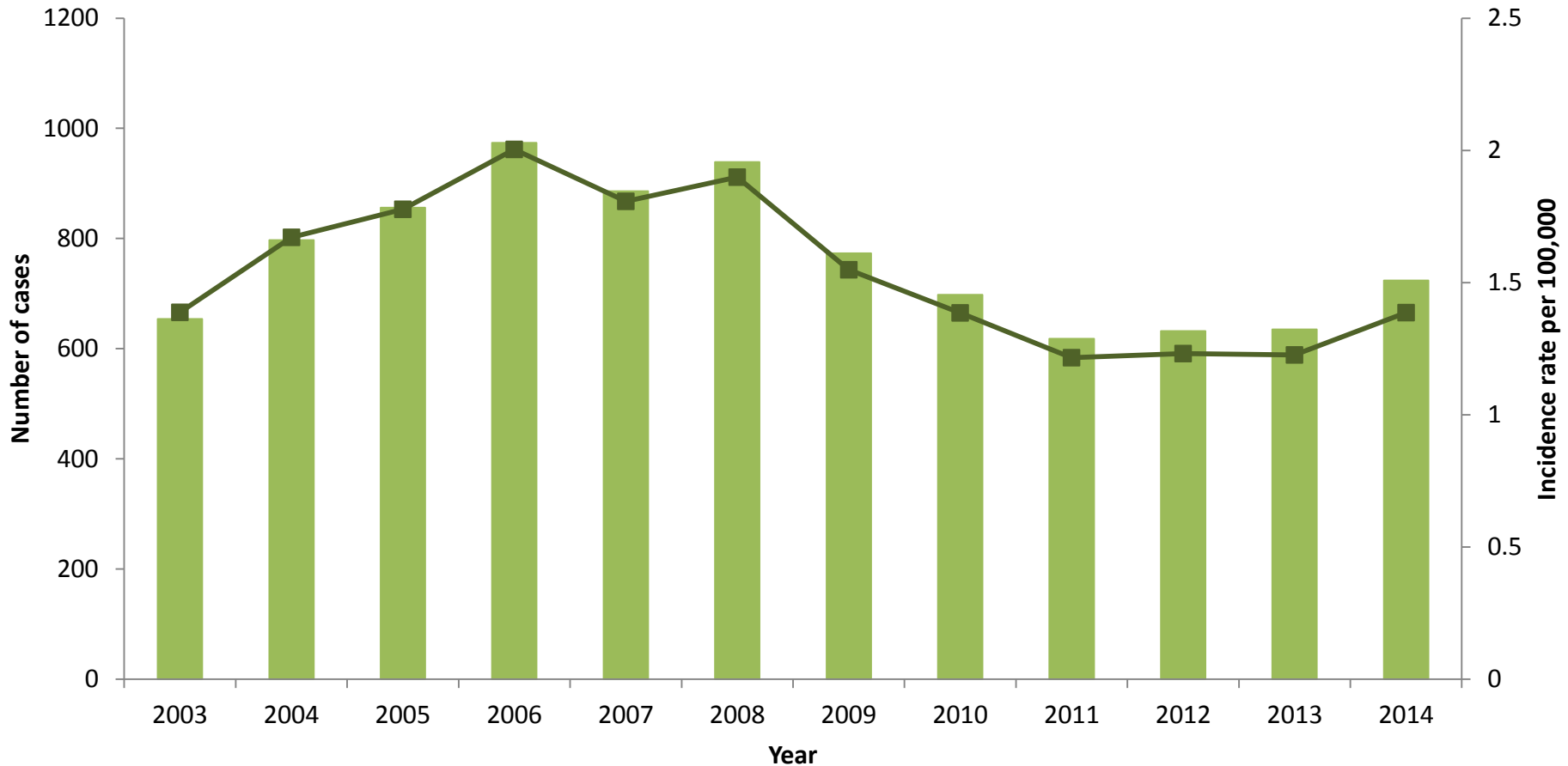
\*\*Laupland *et al*; 2010

# Age-related incidence: Global Burden of iNTS

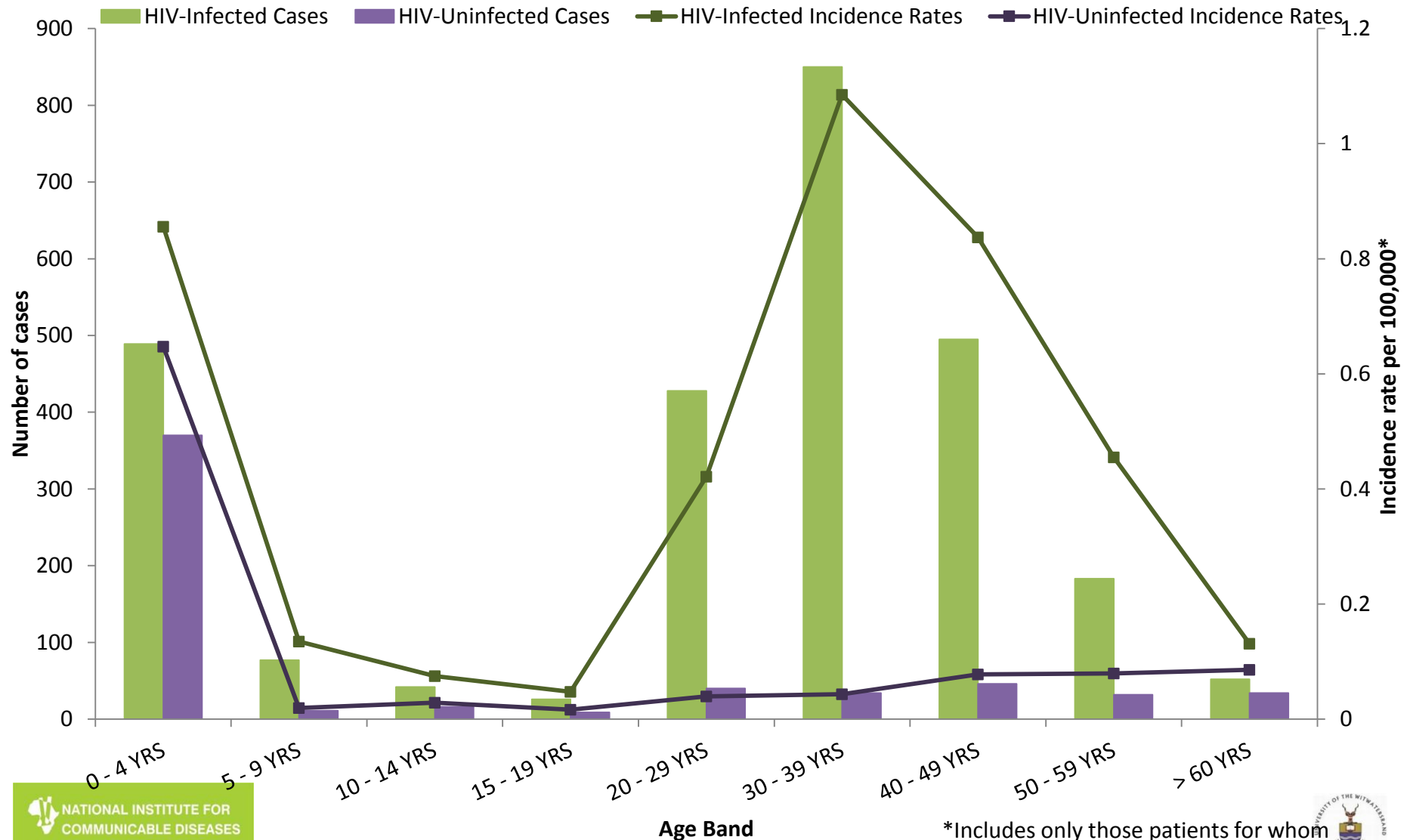


# Invasive *Salmonella* cases, South Africa; 2003 - 2014

Number of cases    Incidence rate per 100,000



# South African experience 2003 - 2013





# iNTS in HIV-uninfected population 2003-2013 in South Africa

- 594/3242 (18.3%) cases
- Commonest serotypes *Salmonella* Enteritidis (210; 35.4%) *Salmonella* Typhimurium (188; 31.6%) *Salmonella* Isangi (32; 5.4%) *Salmonella* Dublin (24; 4.0%).
- Associated with HIV-exposure; prematurity and PEM in children.
- Older children & adults: malignancy; DM; corticosteroid therapy; renal disease.
- Focal infections: septic arthritis; abscess.

# 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