Invasive *Salmonella* infections in Africa

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Centre for International Health

Overview

- ***Salmonella* basics**
- **Typhoidal *Salmonella* in Africa**
- **Invasive non-typhoidal *Salmonella* disease in Africa**
  - **Hazards Associated with Zoonotic enteric pathogens in Emerging Livestock meat pathways (HAZEL)**

Salmonella enterica basics

- **Typhoidal *Salmonella***
  - ***Salmonella enterica* serovars Typhi, Paratyphi A**
  - **Human host restricted**
  - **Fever, bloodstream infection: typhoid and paratyphoid (enteric) fever**
  - **Case fatality ratio ~1%**

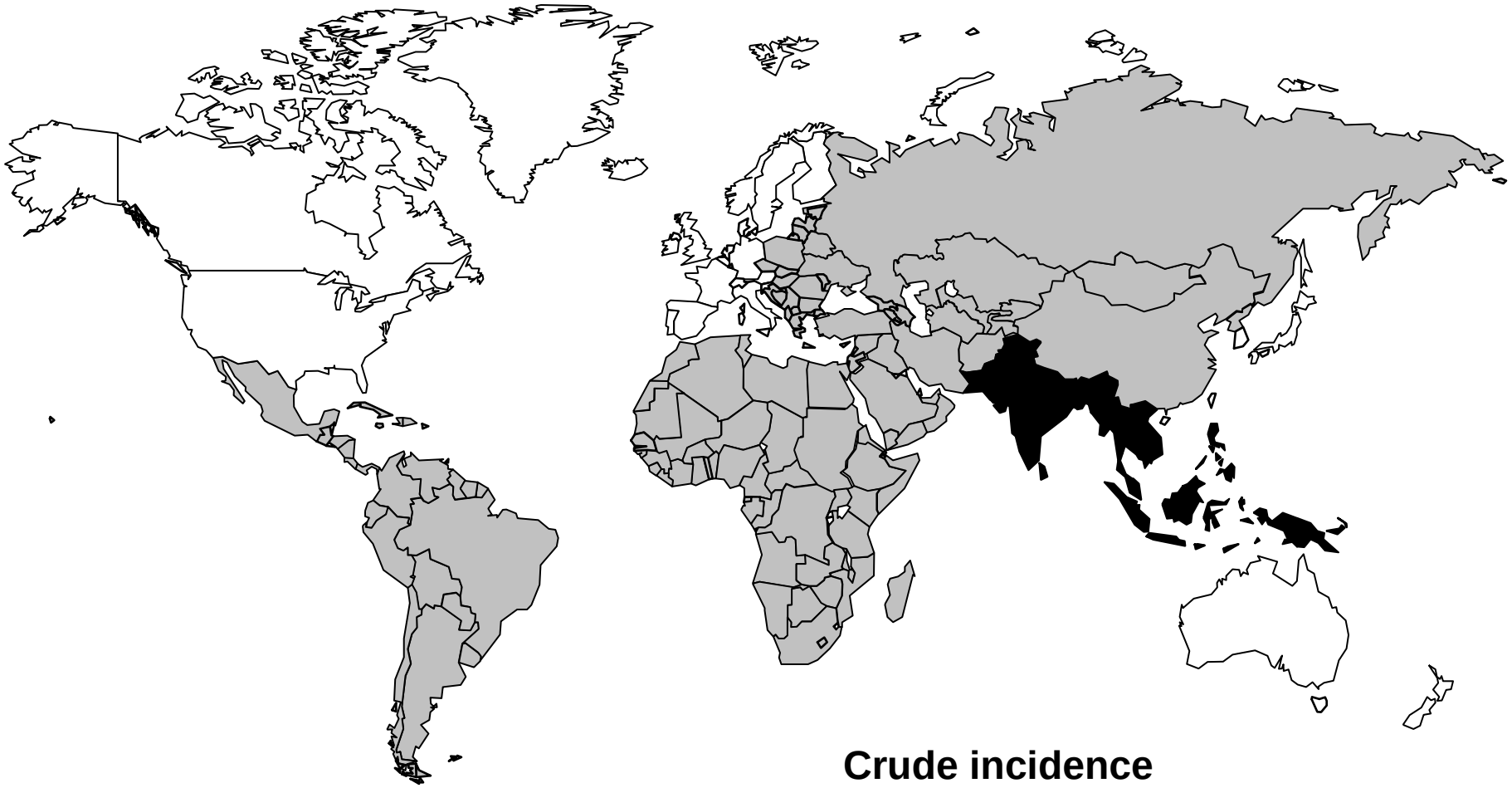
- **Non-typhoidal *Salmonella***
  - **>2,500 serovars e.g., Typhimurium, Enteritidis**
  - **Non-human animals: generalist, host adapted, host restricted**
  - **Diarrheal disease in industrialized countries**
  - **Fever, bloodstream infection in Africa, ~20% case fatality ratio**

Typhoidal *Salmonella* in Africa

- **Typhoid incidence in Africa south of Sahara lower than south and south east Asia**

- **Expanded surveillance studies**
  - **Incidence higher than previously thought in some areas**

Typhoid fever incidence by country, 2000

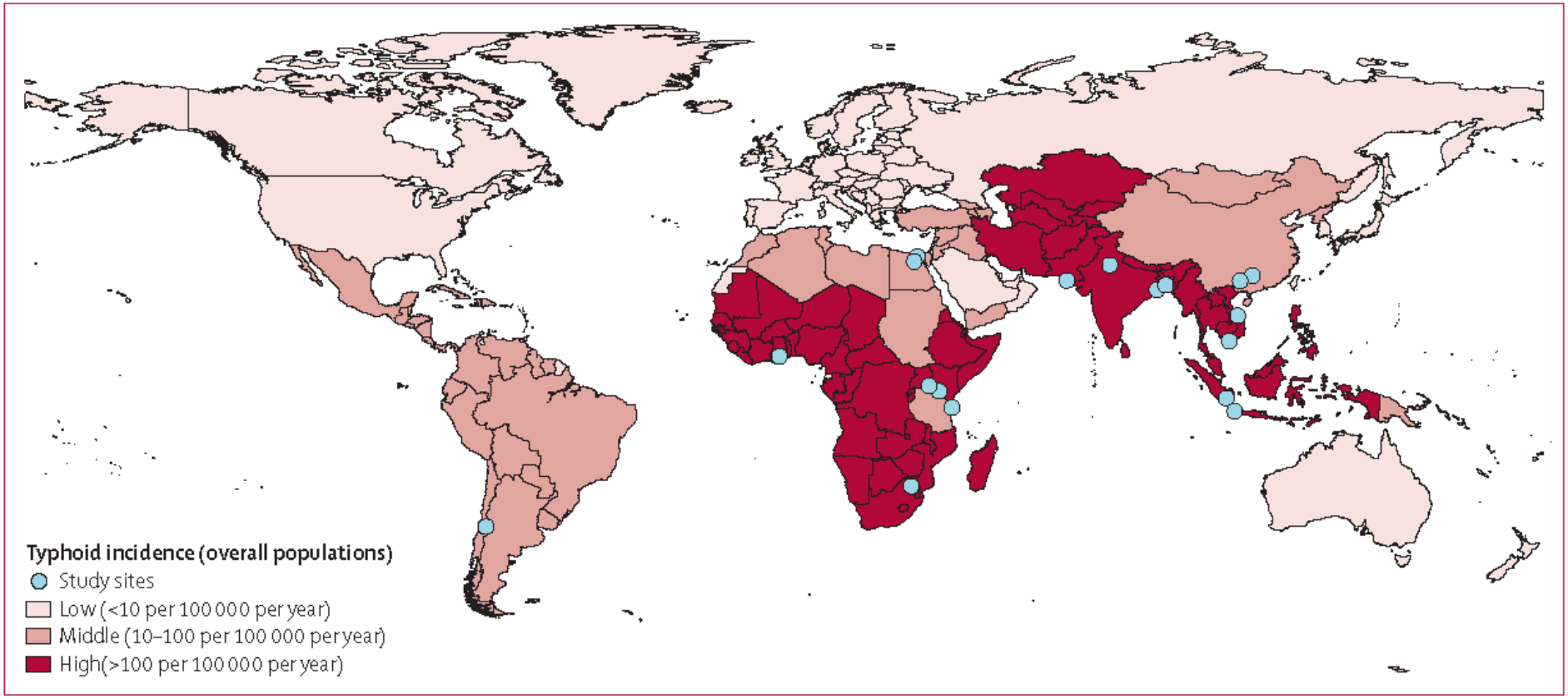


Crude incidence

- **High (>100/100,000/year)**
- **Medium (10-100/100,000/year)**
- **Low (<10/100,000/year)**

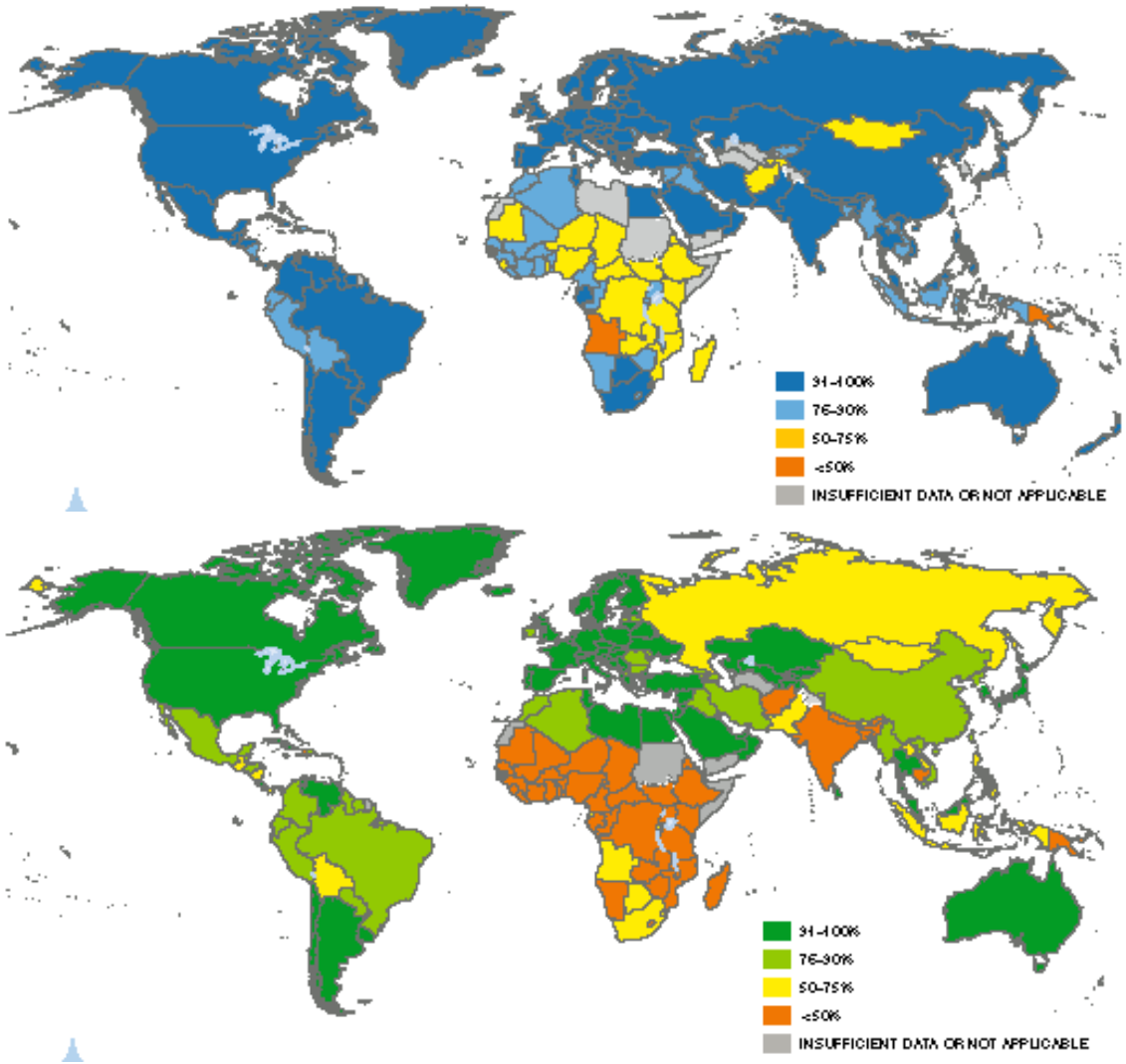
Crump JA, et al. Bull World Health Organ 2004; 82: 346-53

Typhoid fever incidence by country, 2010

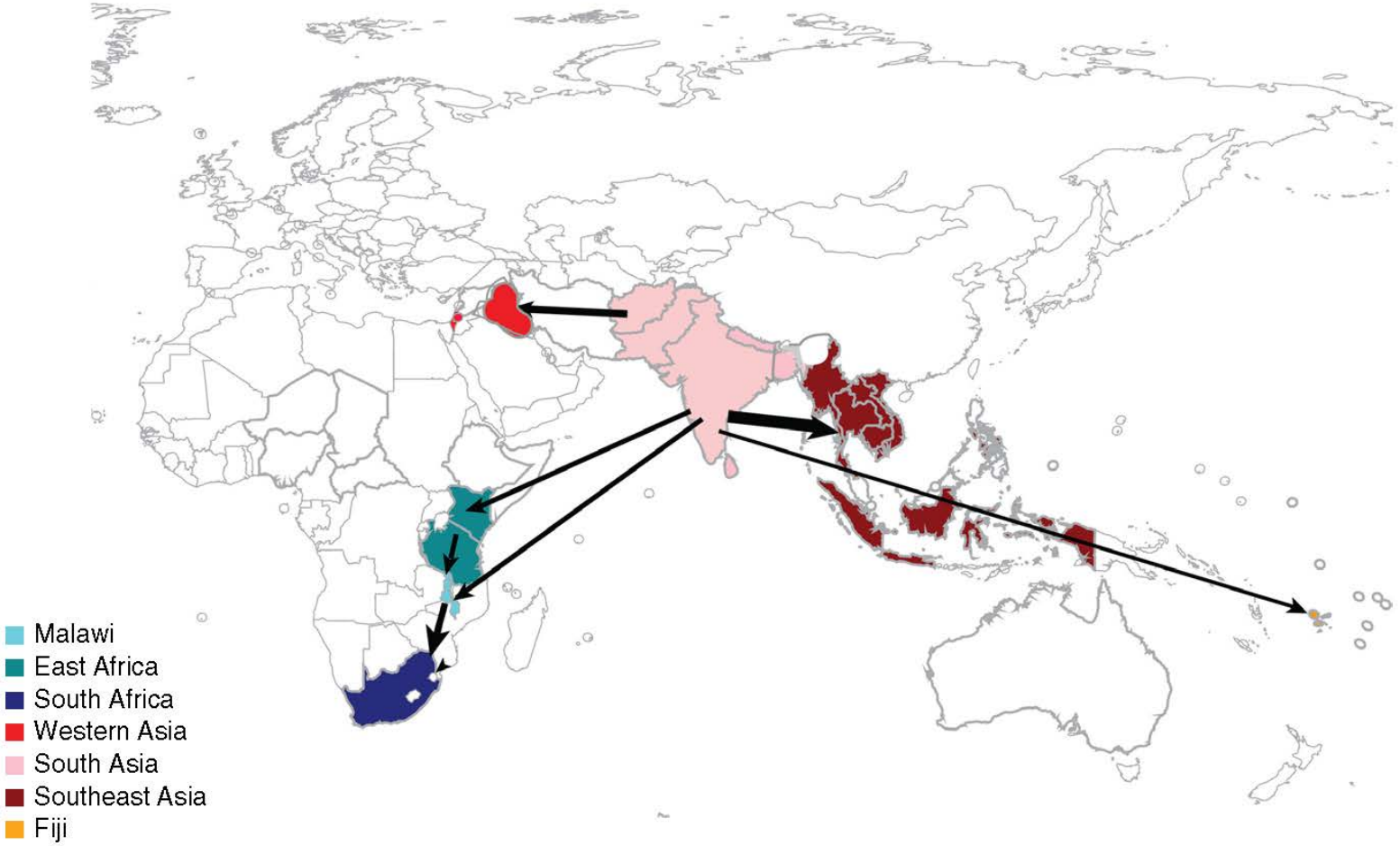


Mogasale V, et al. Lancet Glob Health 2014; 2: e570-80

Proportion of population with access to improved drinking water and sanitation, 2015

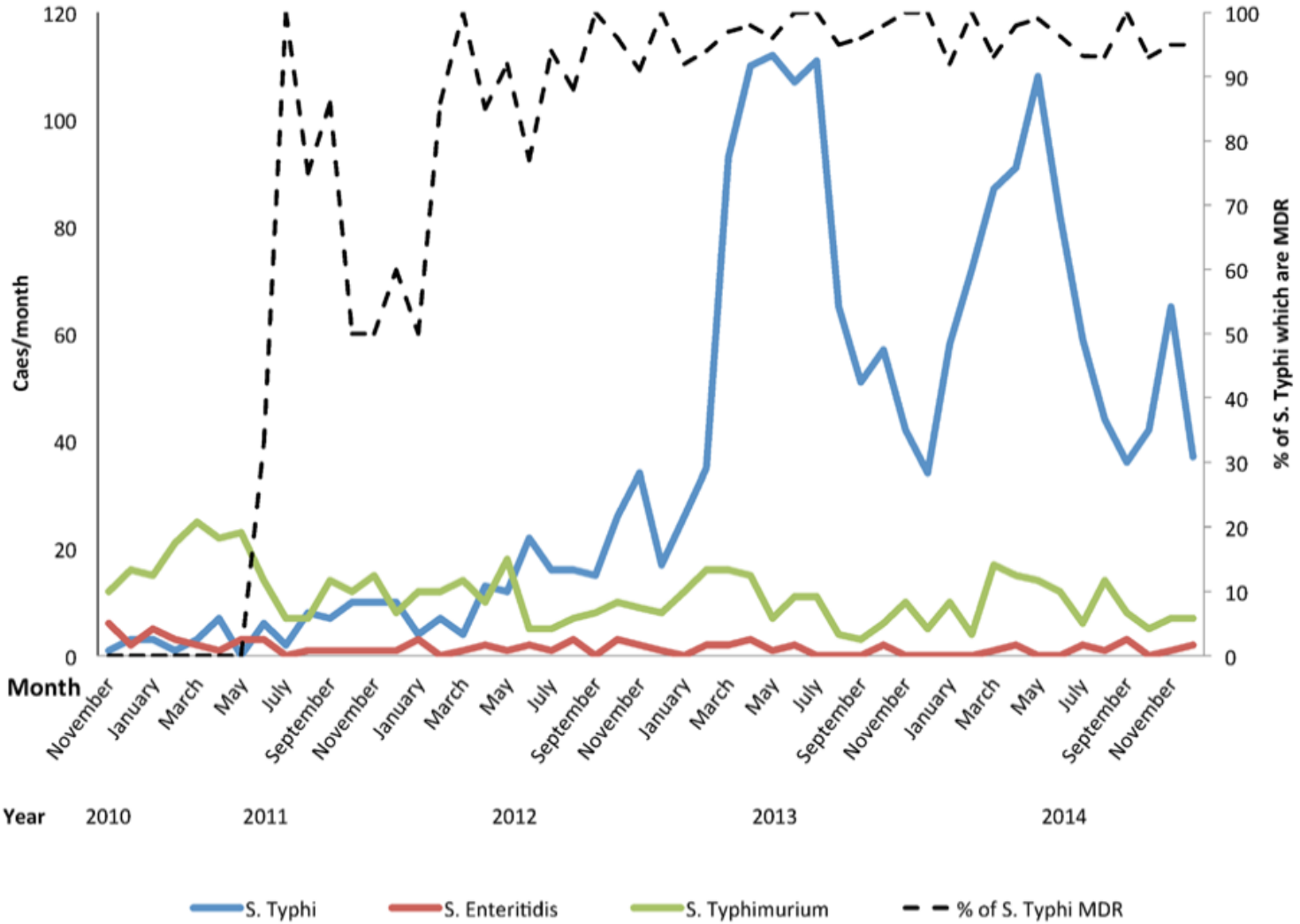


Major geographical transfers of *Salmonella* Typhi H58



Wong VK, et al. Nat Genet 2015; 47: 632-9

Monthly trends *Salmonella* bloodstream infections, Blantyre, Malawi, 2010-2014



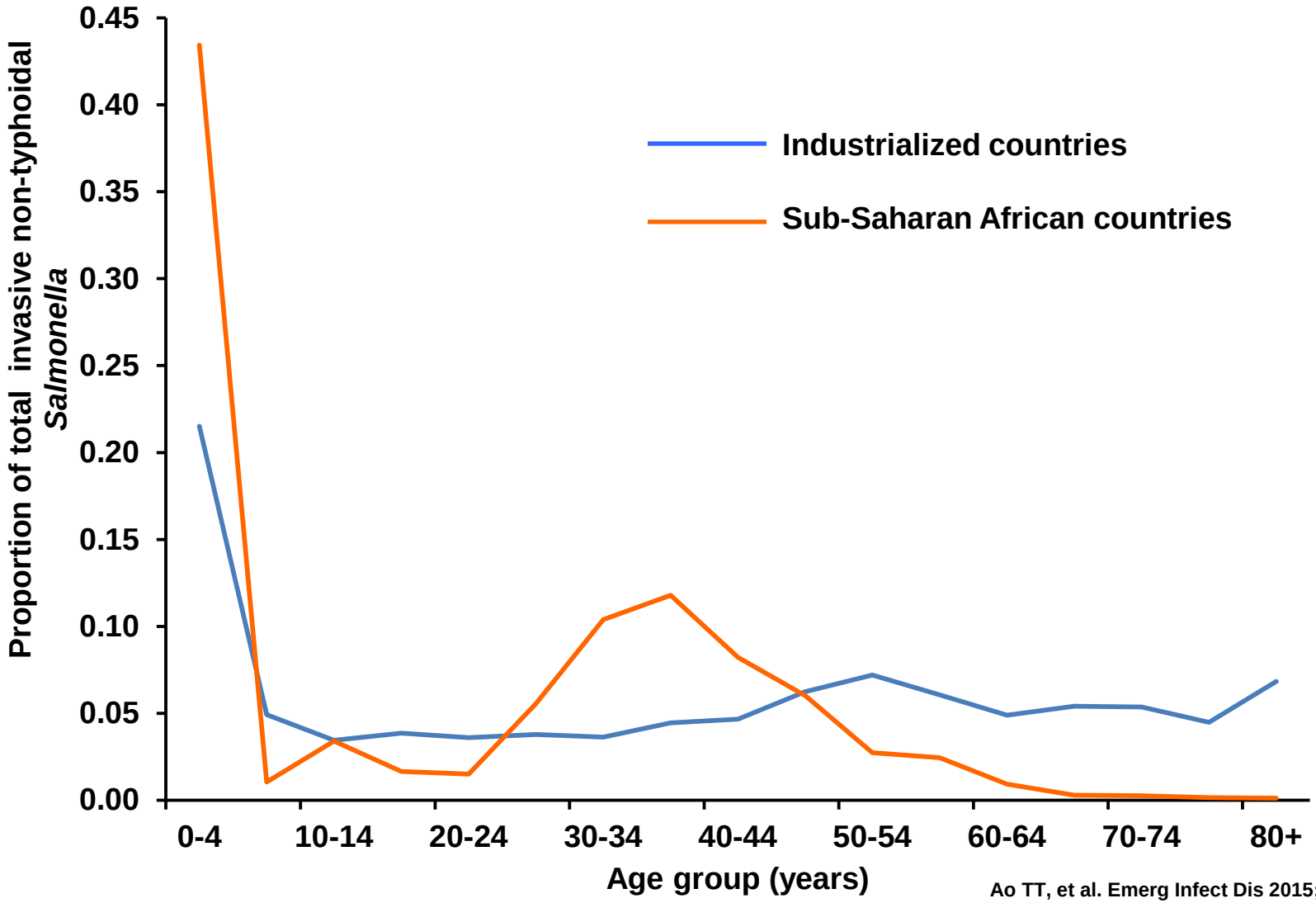
Feasey NA, et al. PLoS Neglect Trop Dis 2015; 9: e0003748

Non-typhoidal *Salmonella* infection in humans

- **Industrialized countries**
  - **Foodborne transmission**
  - **Common cause of self-limited diarrhea**
  - **Occasionally invasive disease: infants, elderly, immunocompromised**

- **Sub-Saharan Africa**
  - **Transmission vehicles poorly understood**
  - **Leading community-acquired bloodstream infection**
  - **Uncommon cause of moderate to severe diarrhea**

Proportion invasive NTS by age, industrialized and sub-Saharan African countries



Ao TT, et al. Emerg Infect Dis 2015; 21: 941-9

Global incidence of enteric and invasive NTS, 2009 and 2010

	Enteric NTS 2009			Invasive NTS 2010		
Region	Population (000s)	Cases	Incidence (/100,000)	Population (000s)	Cases	Incidence (/100,000)
North Africa/Middle East	410,800	563,000	140	446,721	3,617	<1
Africa	767,239	2,458,000	320	854,091	1,942,776	227
Asia/Oceania	1,628,815	53,610,000	3,280	1,693,046	13,920	<1
Southeast Asia	2,072,274	29,839,000	1,440	2,220,248	472,263	21
Europe	738,071	5,065,000	690	746,372	763,191	102
Americas	888,437	2,222,000	250	934,132	210,811	23
GLOBAL	6,511,638	93,757,000	1,140	6,894,610	3,406,579	49

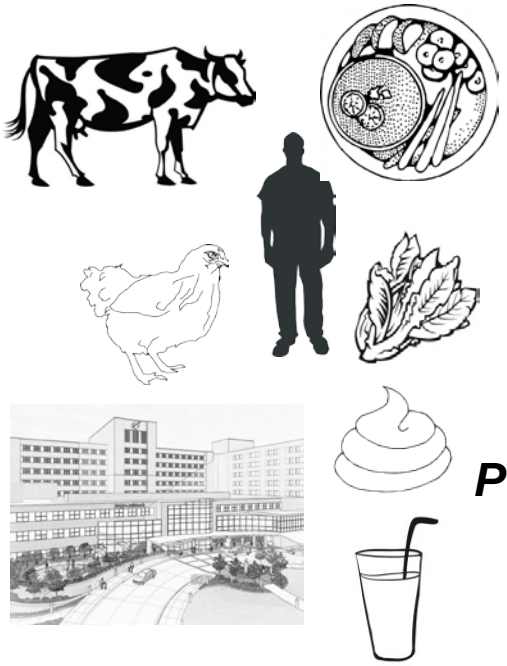
Majowicz SE, et al. Clin Infect Dis 2010; 50: 882–889
Ao TT, et al. Emerg Infect Dis 2015; 21: 941-9

Invasive non-typhoidal *Salmonella* death estimates in context

Condition	Year	Source	Deaths
Enteric NTS	2009	Majowicz SE	155,000
Typhoid and paratyphoid fevers	2010	GBD	190,200
Invasive NTS disease	**2010**	**Ao TT**	**681,316**
Protein-energy malnutrition	2010	GBD	599,800
Malaria	2010	GBD	1,169,500
HIV	2010	GBD	1,465,400

Majowicz SE, et al. Clin Infect Dis 2010; 50: 882–889
Ao TT, et al. Emerg Infect Dis 2015; 21: 941-
Lozano R, et al. Lancet 2012; 380: 2095-128

Pathway to invasive NTS in sub-Saharan Africa



Exposures

Environmental risk factors

Poorly understood

NTS infection/colonization

Host risk factors

Well understood

Invasive NTS disease

Conclusions

- **Typhoid fever appears to be a growing problem in Africa**
  - **Highly receptive due to poor improved water and sanitation coverage**
  - **Arrival of *Salmonella* Typhi H58 coincides increased incidence, epidemics**

- **Invasive non-typhoidal *Salmonella* disease**
  - **Highest incidence in infants, young children, and young adults**
  - **Large number of deaths**
  - **Incomplete understanding of sources, limiting prevention efforts**

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Clinical Infectious Diseases

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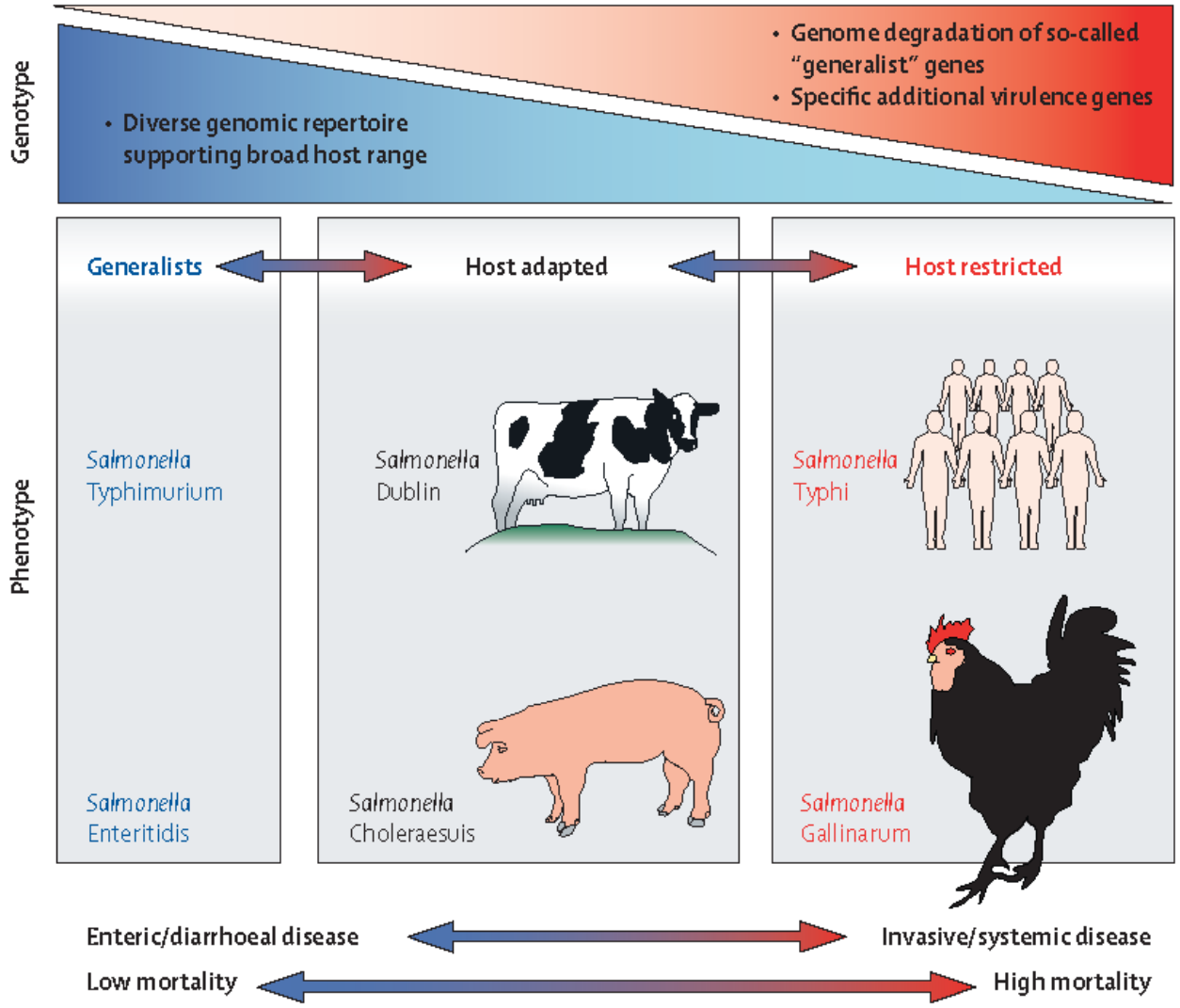
Host adaptation among *Salmonella* and clinical syndrome in the host

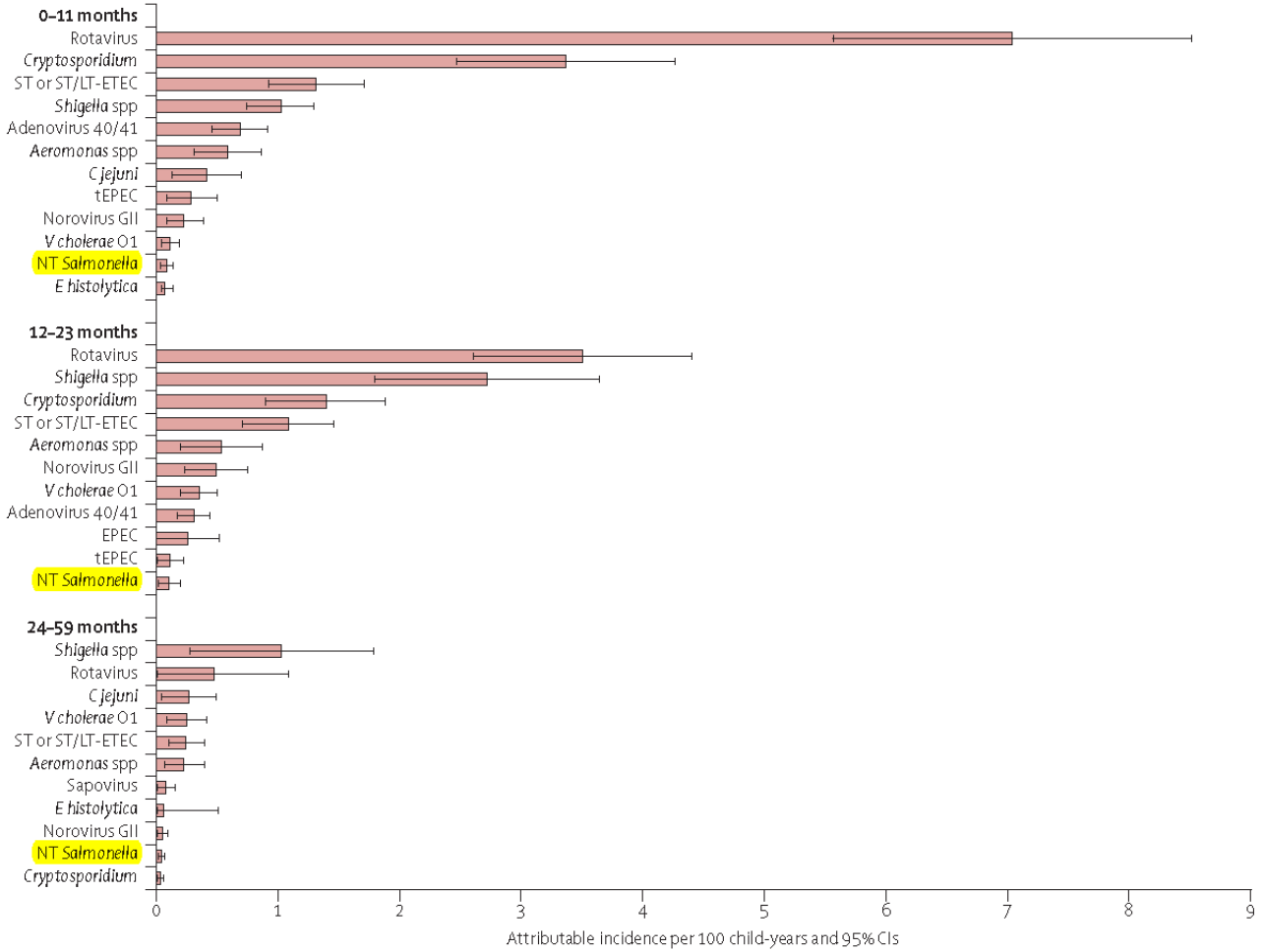


Feasey NA, et al. Lancet 2012; 379: 2489-99

Clinical disease

- **Bacteremia with sepsis**
  - **Fever 95%**
  - **No apparent focus 35%**
- **Non-specific presentation**
  - **Diarrhea 20-50%, not prominent**
  - **Pneumonia 60% children, 30% adults**
  - **Splenomegaly 30-45%**
  - **Hepatomegaly 15-35%**
- **Case fatality ratio high**
  - **20-25%**
- **Recurrence 20-30%**
  - **80% due to recrudescence**

Attributable incidence of pathogen-specific moderate-to-severe diarrhea per 100 child-years by age stratum, all sites combined



Kotloff KL, et al. Lancet 2013; 382: 209-22

Host risk factors

- **Age**
  - **Infants and young children**
- **Malaria**
  - **Recent malaria > current malaria**
  - **Severe malarial anemia**
  - **Sickle cell disease**
  - **Not with cerebral malaria**
- **Malnutrition**
  - **Severe acute malnutrition**
- **HIV**
  - **CD4-positive T-lymphocyte count <200 cells/mm^3**

Section of Tropical Diseases and Parasitology.

[*November* 7, 1929.]

Paratyphoid C an Endemic Disease of British Guiana : A Clinical and Pathological Outline. *B. paratyphosum* C as a Pyogenic Organism : Case Reports.

By GEORGE GIGLIOLI, M.D.

of which 80 were confirmed bacteriologically by isolation of the specific organism from the blood during life, or from the spleen post mortem. The disease appears to be endemic in the Colony, with a tendency to occasional epidemic outbursts, two of which were observed in 1924 and 1926 respectively, in coincidence with important malarial outbreaks.

Giglioli G. Proc R Soc Med 1929; 23: 165-177

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 155, NO. 6 • JUNE 1987
 0022-1899/87/5506-0031$01.00

Plasmodium falciparum Malaria and *Salmonella* Infections in Gambian Children

Mabey DC, et al. J Infect Dis 1987; 155: 1319-21

Malaria and invasive NTS

- **Invasive NTS incidence varies in space with malaria transmission intensity**
  - **Moshi vs. Teule, Tanzania**
  - **Nairobi vs. Kisumu, Kenya**

- **iNTS incidence varies in time with malaria transmission intensity**
  - **Rising malaria: Kisumu, Kenya**
  - **Declining malaria: Fajara and Basse, Gambia; Teule, Tanzania**

Biggs HM, et al. Clin Infect Dis 2014; 58: 638-47
Tabu C, et al. PLoS One 2012; 7: e31237
MacKenzie G, et al. PLoS One 2010; 5: e10568
Mtove G, et al. Malar J 2011; 10: 320

Mechanism for malaria and invasive NTS association

- Hemolysis-associated neutrophil dysfunction
- Parasite-induced IL-12 reduction
- Free iron
- Increased gut permeability
- Perturbation of the gut flora by sulfadoxine-pyrimethamine

HIV and invasive NTS

- **Proportion of invasive NTS cases with HIV-infection**
  - **Infants and children: 20%**
  - **Adolescents and adults: 95%**

- **Mechanisms**
  - **Loss on IL-17 producing CD4 cells in gut mucosa**
  - **Excess anti-LPS IgG inhibiting serum killing of extracellular *Salmonella***
  - **Dysregulation of proinflammatory cytokine response allowing intracellular survival and persistence**

Gilks CF, et al. Lancet 1990; 336: 545-9
Brent AJ, et al. Pediatr Infect Dis J 2006; 25: 230-6

The pathogen

- ***Salmonella*** **Typhimurium ST 313**

- **Genomic features of human host adaptation**
  - **Genome degradation**
  - **Not host restricted**
  - **Will infect and cause disease in poultry**

- **Antimicrobial resistance**
  - **Ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol**
  - **Fluoroquinolones**
  - **Extended spectrum cephalosporins**

Kingsley RA, et al. Genome Res 2009; 19: 2279-87
Parsons BN, et al. PLoS Neglect Trop Dis 2013; 7: e2487

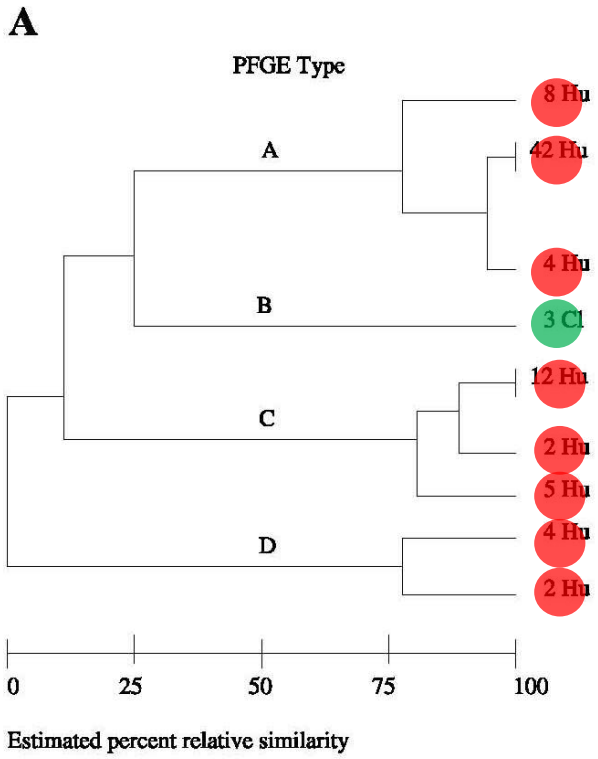
Environmental risk factors

- **Industrialized country paradigm**
  - **Food animal products**
  - **Feces contaminated produce and water**
  - **Direct and indirect animal contact**

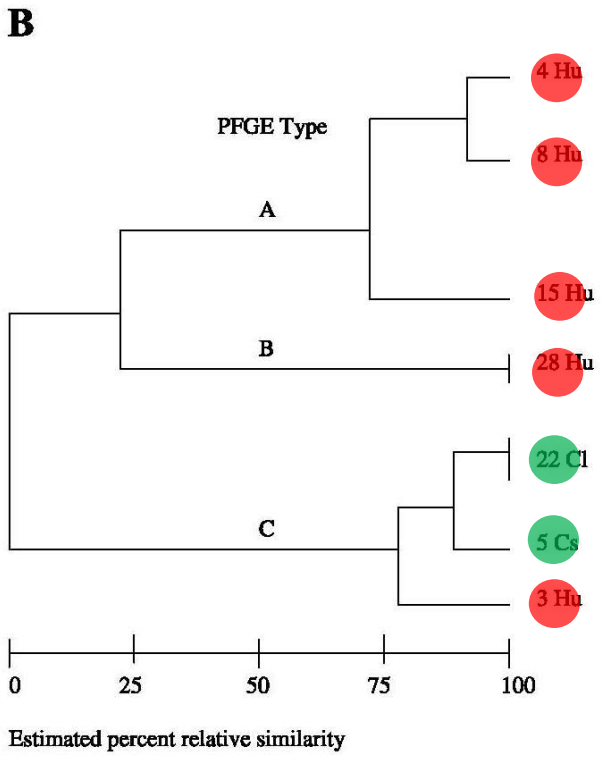
- **Sub-Saharan African country challenges**
  - **Little epidemiologic research**
  - **Understanding infection/colonization**
  - **Genomic data suggest human host adaptation**

Molecular relatedness of NTS isolated from humans and their peridomestic animals

Salmonella Typhimurium



Salmonella Enteritidis



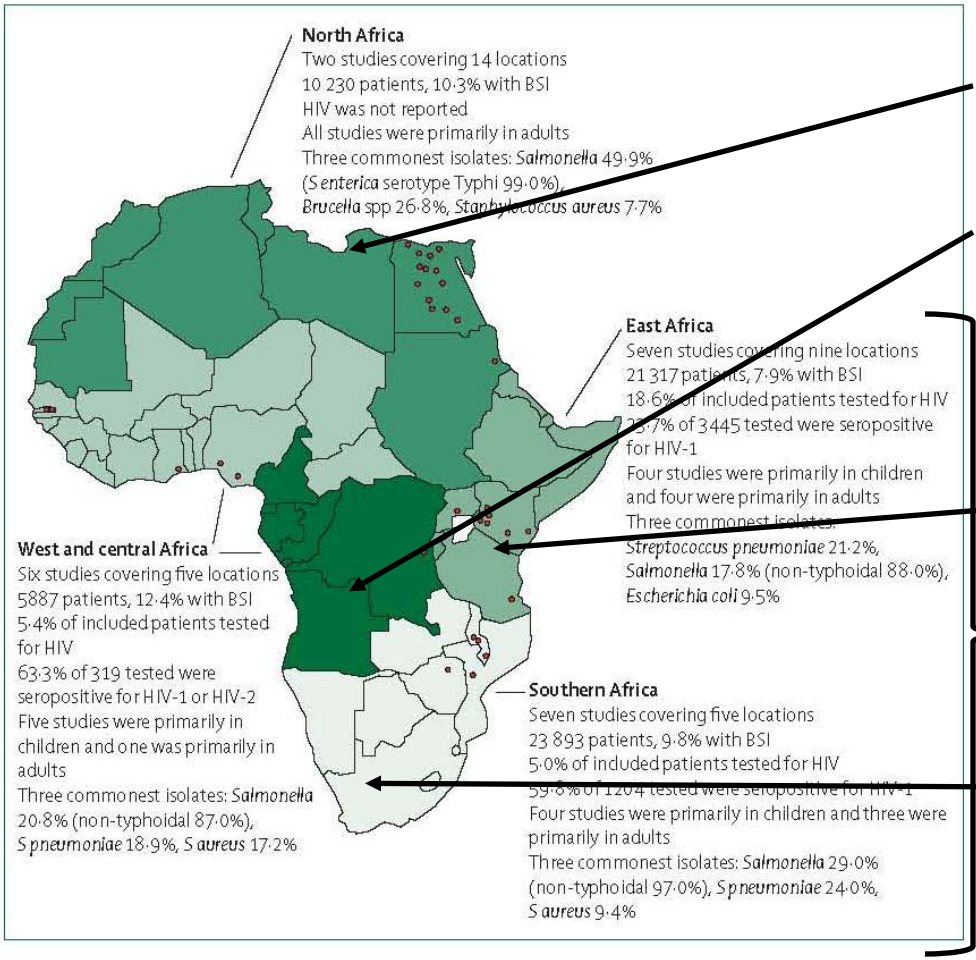
Kariuki S, et al. FEMS Immunol Med Microbiol 2002; 33: 165

Vaccines

- **Polysaccharide Vi**
  - **Glycoconjugate polysaccharide-protein**
  - **Expand to relevant O and H antigens**
- **Live attenuated Ty21a**
  - **New live attenuated vaccines, multiple serovars**
- **Whole cell inactivated**
  - **Generalized Modules for Membrane Antigens (GMMA)**
  - **Recombinant purified protein**
  - **Select cross-protecting recombinant or purified proteins**
- **Host factors**
  - **Immunogenicity**
  - **Safety (live attenuated)**

MacLennan CA, et al. Hum Vaccin Immunother 2014; 10: 1478-93

Community-acquired bloodstream infections, Africa



North Africa (n=10,230)

- ***Salmonella enterica* 50% (99% Typhi)**
- ***Brucella* spp *27%***
- ***Staphylococcus aureus* 8%**

West and central Africa (n=5,887)

- ***Salmonella enterica* 21% (87% NTS)**
- ***Streptococcus pneumoniae* 19%**
- ***Staphylococcus aureus* 17%**

East Africa (n=21,317)

- ***Streptococcus pneumoniae* 21%**
- ***Salmonella enterica* 18% (88% NTS)**
- ***Escherichia coli* 17%**

Non-typhoidal *Salmonella* serovars

- **Typhimurium***
- **Enteritidis***
- **Stanleyville**
- **Dublin**
- **Isangi**

Southern Africa (n=23,893)

- ***Salmonella enterica* 29% (97% NTS)**
- ***Streptococcus pneumoniae* 24%**
- ***Staphylococcus aureus* 9%**

Reddy EA, et al. Lancet Infect Dis 2010; 10: 417

Global Enterics Multi-center Study (GEMS)

- **Etiology of moderate to severe diarrheal disease among infants and children <5 years of age in low-income countries**
- **3-year prospective, age stratified, matched case-control study with 7 sites**
  - **9,439 cases and 13,129 controls**
- **Calculated adjusted population attributable fraction**
  - **Accounting for presence of putative pathogens in control group**

Kotloff KL, et al. Lancet 2013; 382: 209-22

NTS and diarrhea in developing countries

	Adjusted attributable fraction (95% CI)						
Age group (months)	Basse The Gambia	Bamako Mali	Manhica Mozambique	Nyanza Kenya	Kolkarta India	Mirzapur Bangladesh	Karachi Pakistan
0-11	-	-	-	-	-	4.2 (2.2, 6.2)	-
12-23	-	-	-	3.2 (0.5, 6.0)	-	-	-
24-59	-	-	-	3.7 (1.2, 6.1)	-	-	-

Kotloff KL, et al. Lancet 2013; 382: 209-22