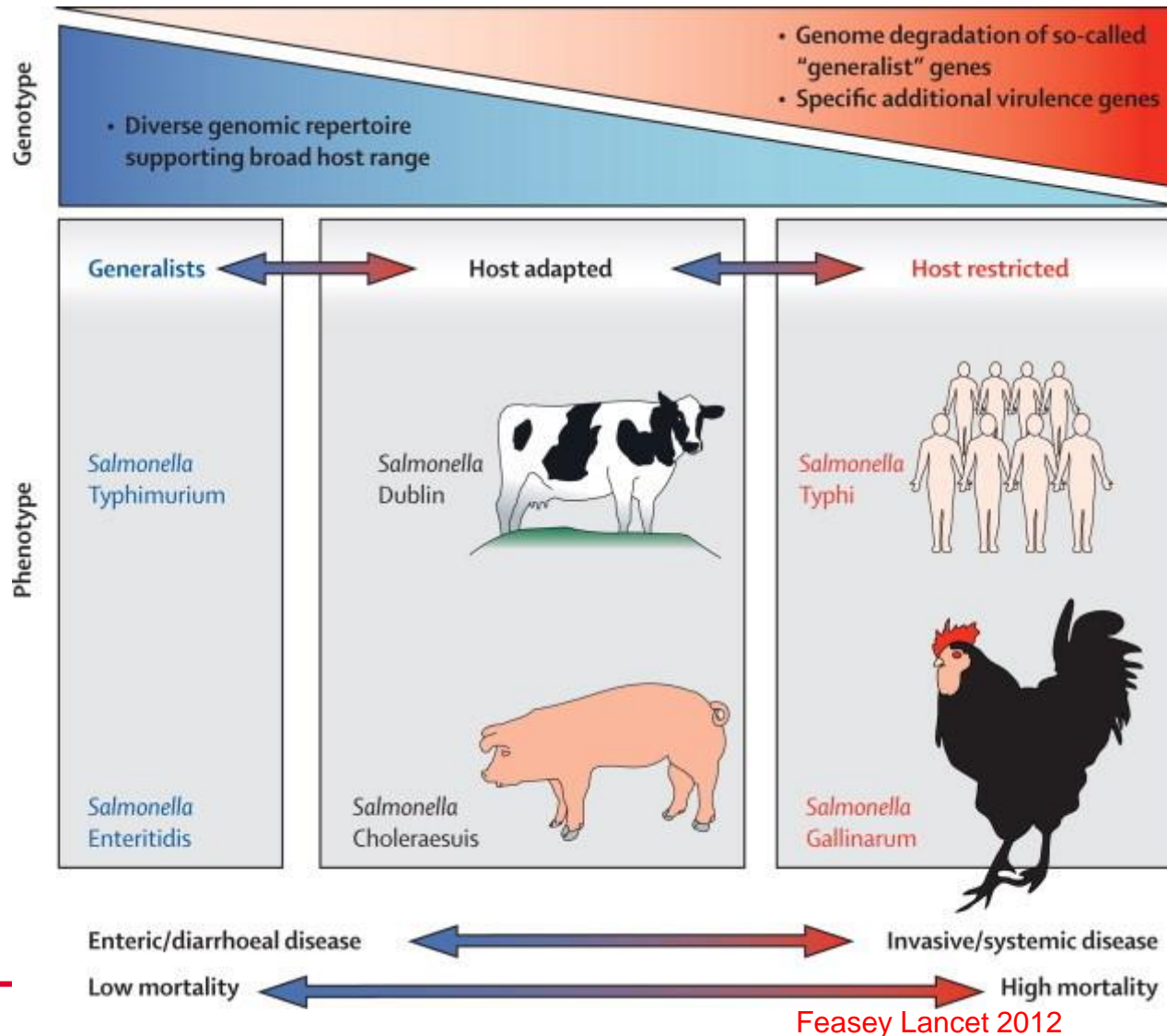




Strains of Salmonella associated with invasive disease

Nick Feasey

Enteric vs invasive lifestyles



Paediatric iNTS disease in Africa: pre/early HIV era



Nigeria, 1970s
Alausa, Scand J Infect Dis

Kenya 1980s
Wamola, E Afr Med J

Gambia 1980s
Mabey, JID

DRC 1980s
Green, Ann Trop Paeds

Rwanda, 1980s
Le Page, Lancet

ACQUIRED IMMUNE DEFICIENCY SYNDROME IN BLACK AFRICANS

IR.—Acquired immune deficiency syndrome (AIDS) has been described in homosexual or bisexual men, in drug addicts, in haemophiliacs, and in Haitian immigrants.¹ To our knowledge there is no report of AIDS and opportunistic infections in previously healthy Black Africans with no history of homosexuality or drug abuse. Tables I and II show the clinical and immunological data on five Black patients seen in Brussels and who were from Central Africa

TABLE I—SEROLOGICAL MARKERS* AND OPPORTUNIST INFECTIONS IN FIVE HETEROSEXUAL BLACK AFRICANS

Case	Virus antibody titres (inverse)				Opportunistic infections
	CMV	EBV			
		VCA	EA	IgM	
A, 33)	0	512	128	4	<i>S. typhimurium</i> septicaemia; disseminated <i>C. neoformans</i>
B, 36)	0	128	4	4	<i>T. gondii</i> brain abscess
C, 26)	16	64	4	4	Herpes simplex type 2; <i>C. albicans</i> oesophagitis
D, 22)	8	ND	ND	ND	Herpes simplex type 2
E, 39)	128	5120	512	0	<i>S. typhimurium</i> septicaemia; <i>C. albicans</i> stomatitis

*CMV = cytomegalovirus; EBV = Epstein-Barr virus (VCA viral capsid antigen, EA early antigen). All four patients tested (not patient D) had antibody to hepatitis B surface antigen.

... (re and Chad). Three of them had been living in Belgium, for ... (reen 8 months and 3 years. All were of good socioeconomic ... (us. They presented with prodromes of fever, weight loss, and ... (eralised lymphadenopathy, and extensive investigations did not ... (al any neoplasia. Patients A and B died; the three survivors are ... (ill.

... (hese patients fulfilled all the criteria of AIDS. Two of them had ... (re herpes simplex infections and to exclude the possible role of ... (es virus in their immune deficiency we did lymphocyte subset ... (yses in a control group of eight patients with HSV-2 infections.

TABLE II—LYMPHOCYTE SUBSET ANALYSES

Case	Lymphocyte count (μ l)	Subset analyses		
		OKT4 ⁺ (%)	OKT8 ⁺ (%)	Ratio
A	209	1	22	0.04
B	1230	3	74	0.04
C	1311	1	52	0.02
D	396	0	26	(0.00)
E	2365	0	57	(0.00)
Normal*	1230-4500	27-65	12-36	1.20-2.25

... (age in eleven healthy age matched Africans.

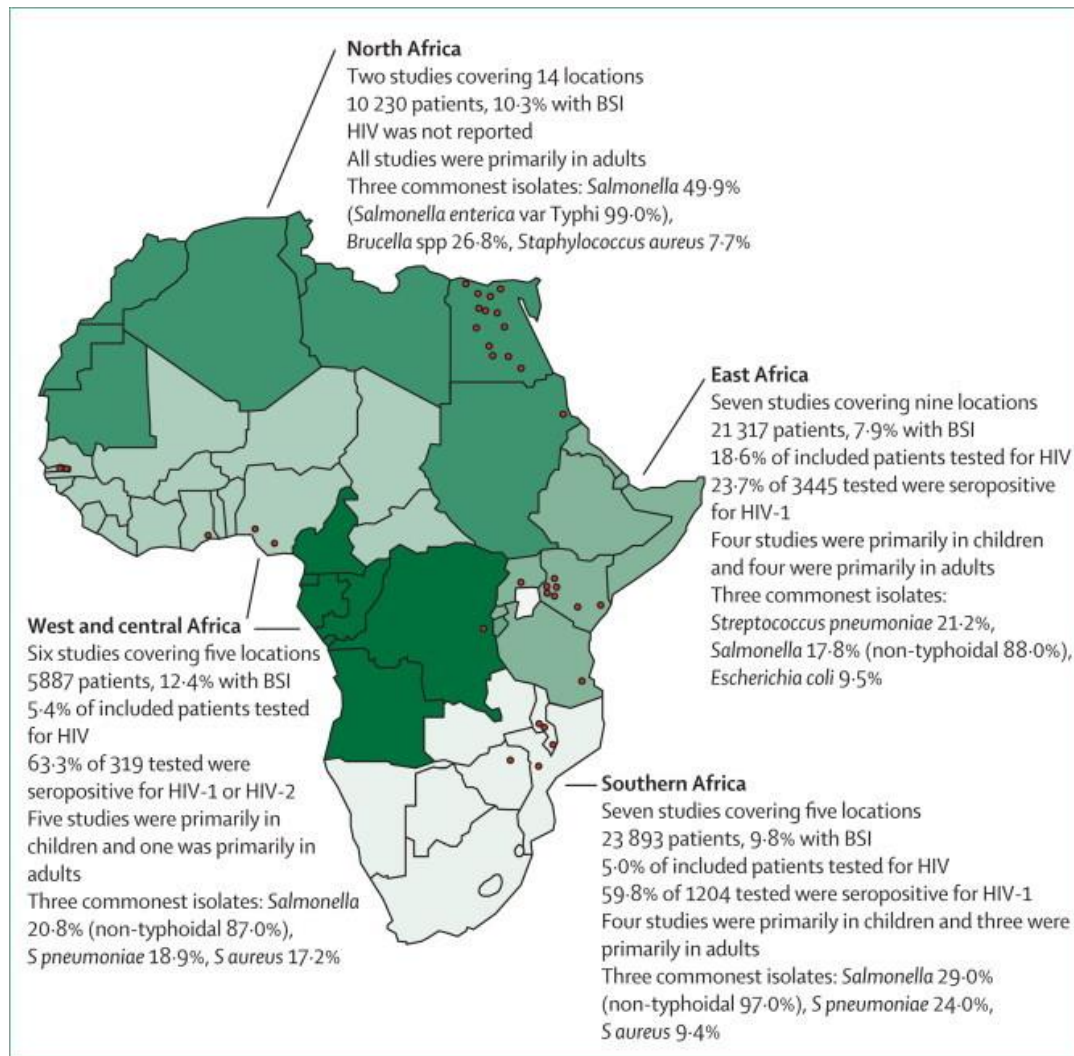
... (e had OKT4⁺ deficiency and their OKT4⁺/OKT8⁺ ratios ... (between 0.99 and 2.52 (mean 1.80), so it is unlikely that ... (-2 alone was responsible for the AIDS in the African patients. ... (sponses to mitogen stimulation (phytohaemagglutinin, ... (anavalin A, pokeweed) were well below normal in all cases. In ... (en healthy Black Africans reactions to intradermal tuberculin, ... (ida, and streptodornase were >5 mm; all five patients were skin ... (negative to these antigens.

... (his preliminary report suggests that Black Africans, immigrants ... (ot, may be another group predisposed to AIDS.

N. CLUMECK
F. MASCART-LEMONE
J. DE MAUBEUGE
D. BRENEZ
L. MARCELIS

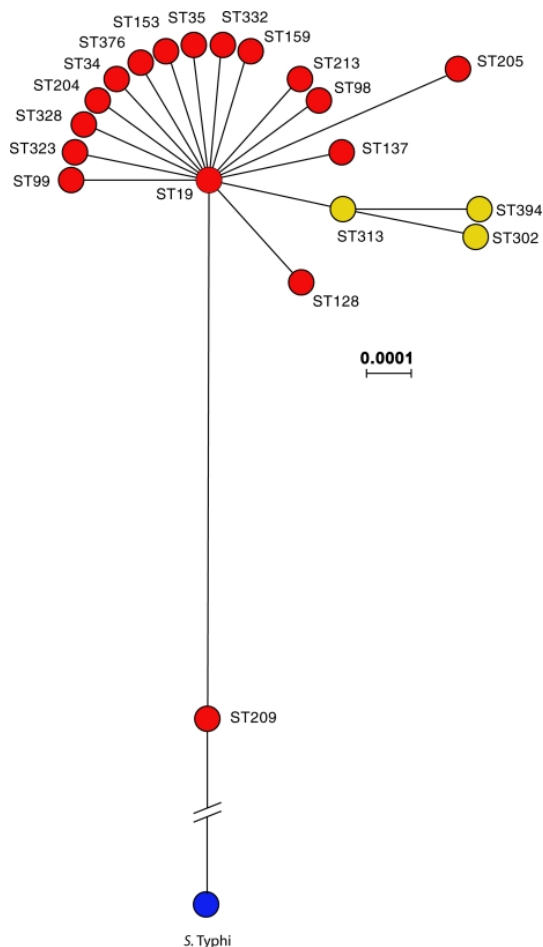
... (ira J, Franck E, Spira TJ, et al. Acquired immune deficiency in Haitians. *N Engl J Med* 1983; 308: 125-29.

INTS disease AIDS defining & NTS among most common cause of bloodstream infection in SSA



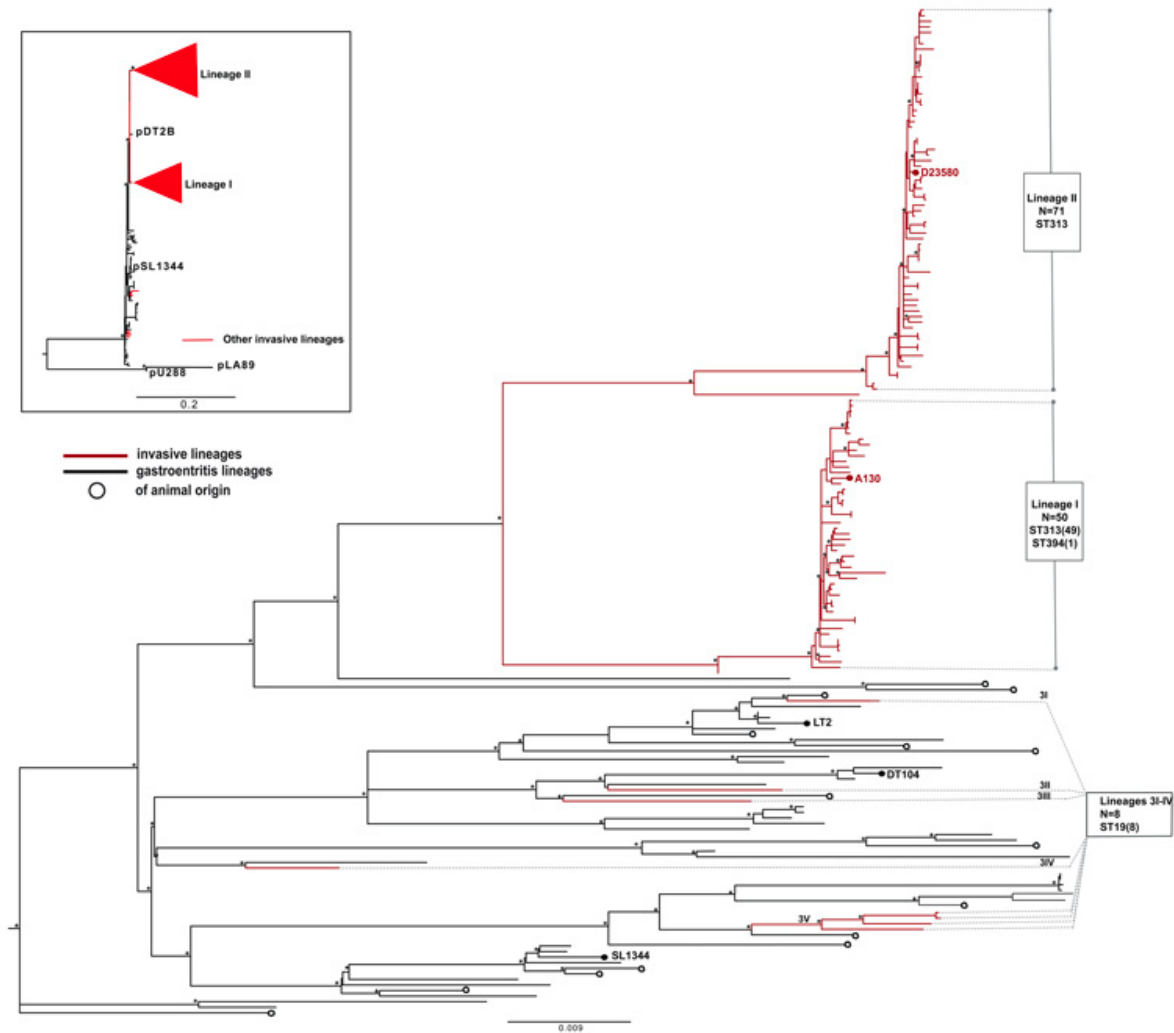


S. Typhimurium associated with iNTS disease in sub-Saharan Africa have novel MLST: ST313

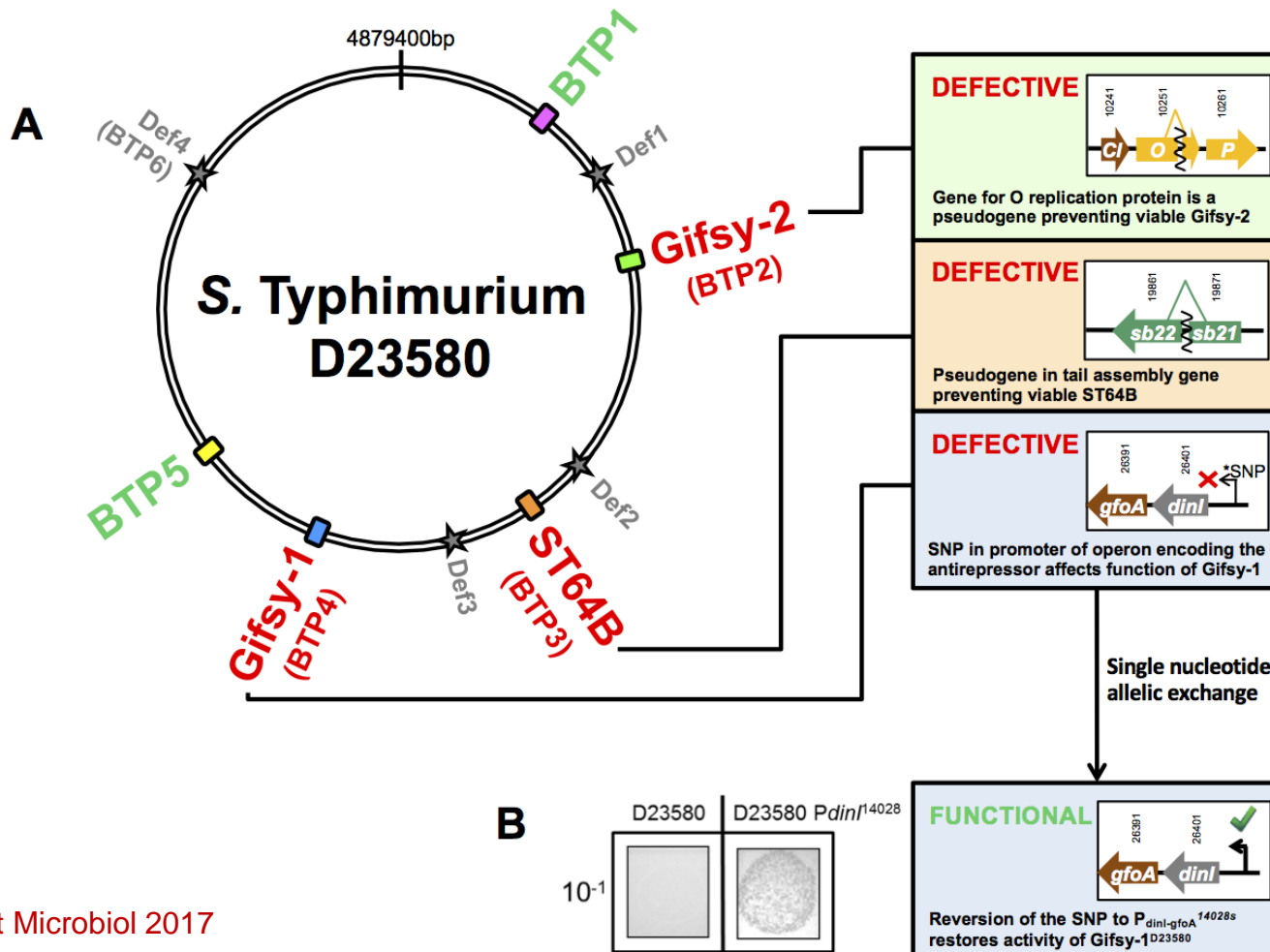


- **Genomic degradation**
 - Also seen in *S. Typhi* and other pathogens becoming host adapted
 - Similar genes to *S. Typhi*
- **Novel Prophage repertoire**
- **MDR cassette in virulence plasmid**

Phylogeny of *S. Typhimurium* reveals isolates from SSA fall into two highly related lineages

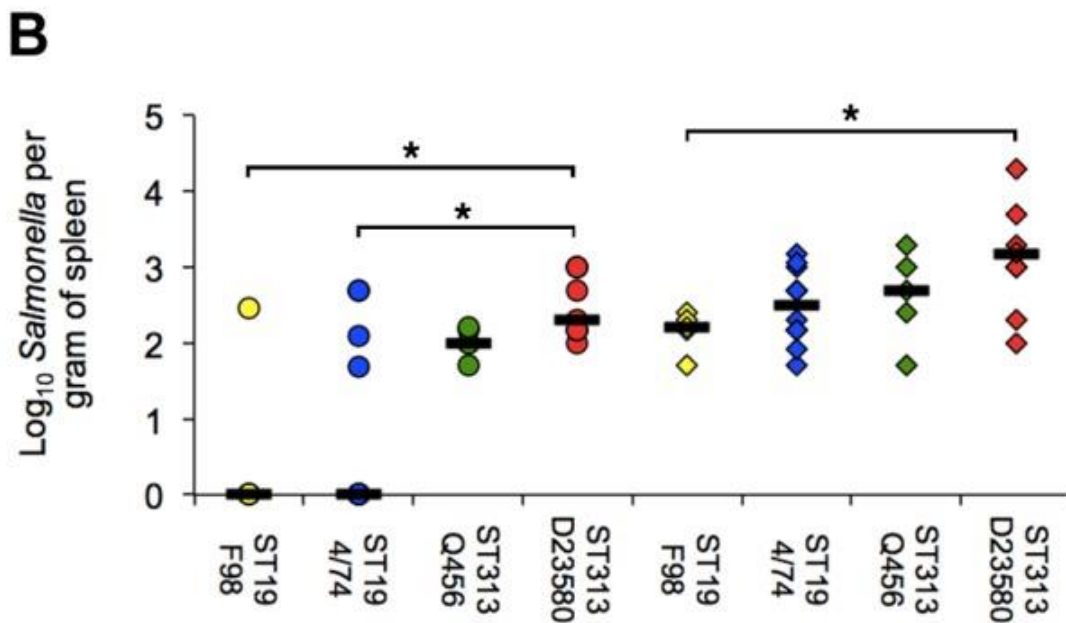
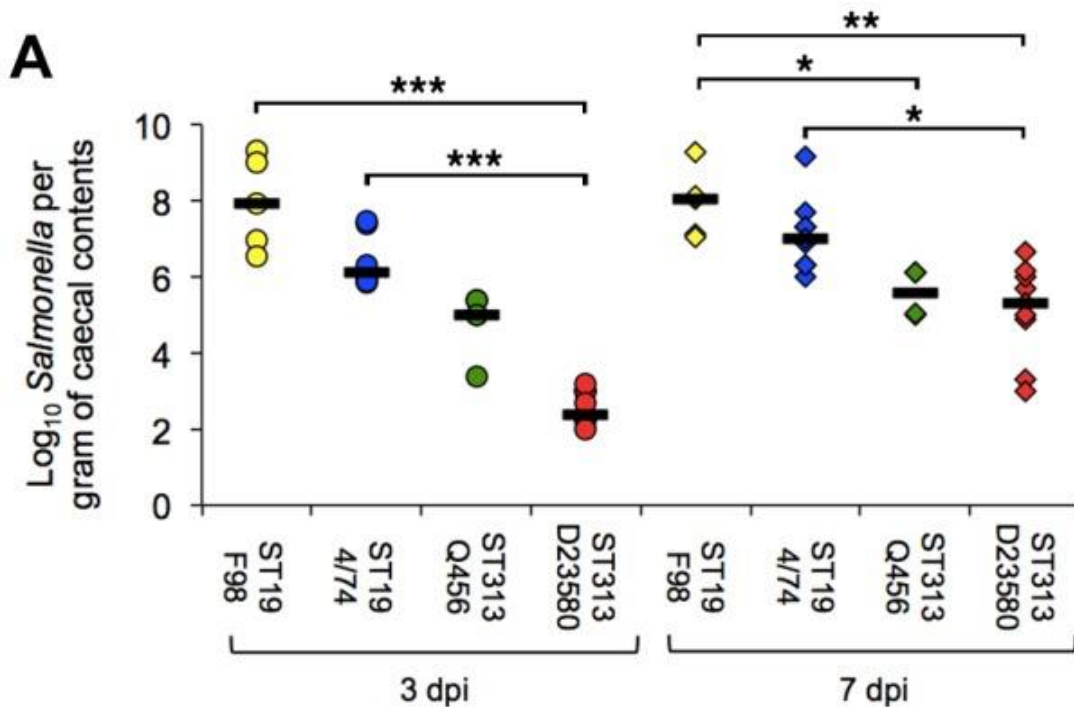


Novel Prophages: Blantyre Type Prophage 1

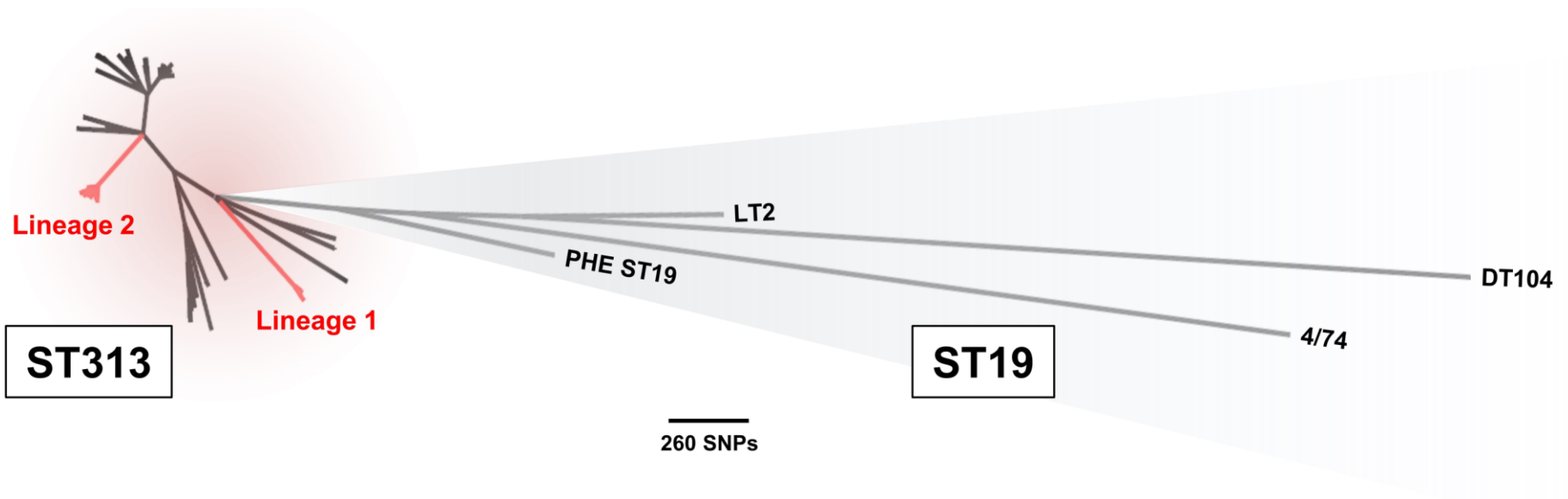


- **ST313-td gene on BTP1 – (Herrero-Freson 2014, Owen 2017)**
- **ST313 stimulate less inflammasome activation than ST19 (Carden 2015)**
- **ST313 with naturally attenuated flagellin elicits reduced inflammation, replicates in macrophages (Ramachandran 2015)**
- **Loss of multicellular behavior in ST313 (Singletary 2016)**
- **Pseudogenization of the Secreted Effector Gene ssel Confers Rapid Systemic Dissemination (Carden 2017)**

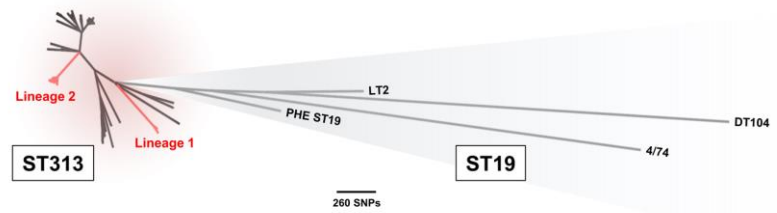
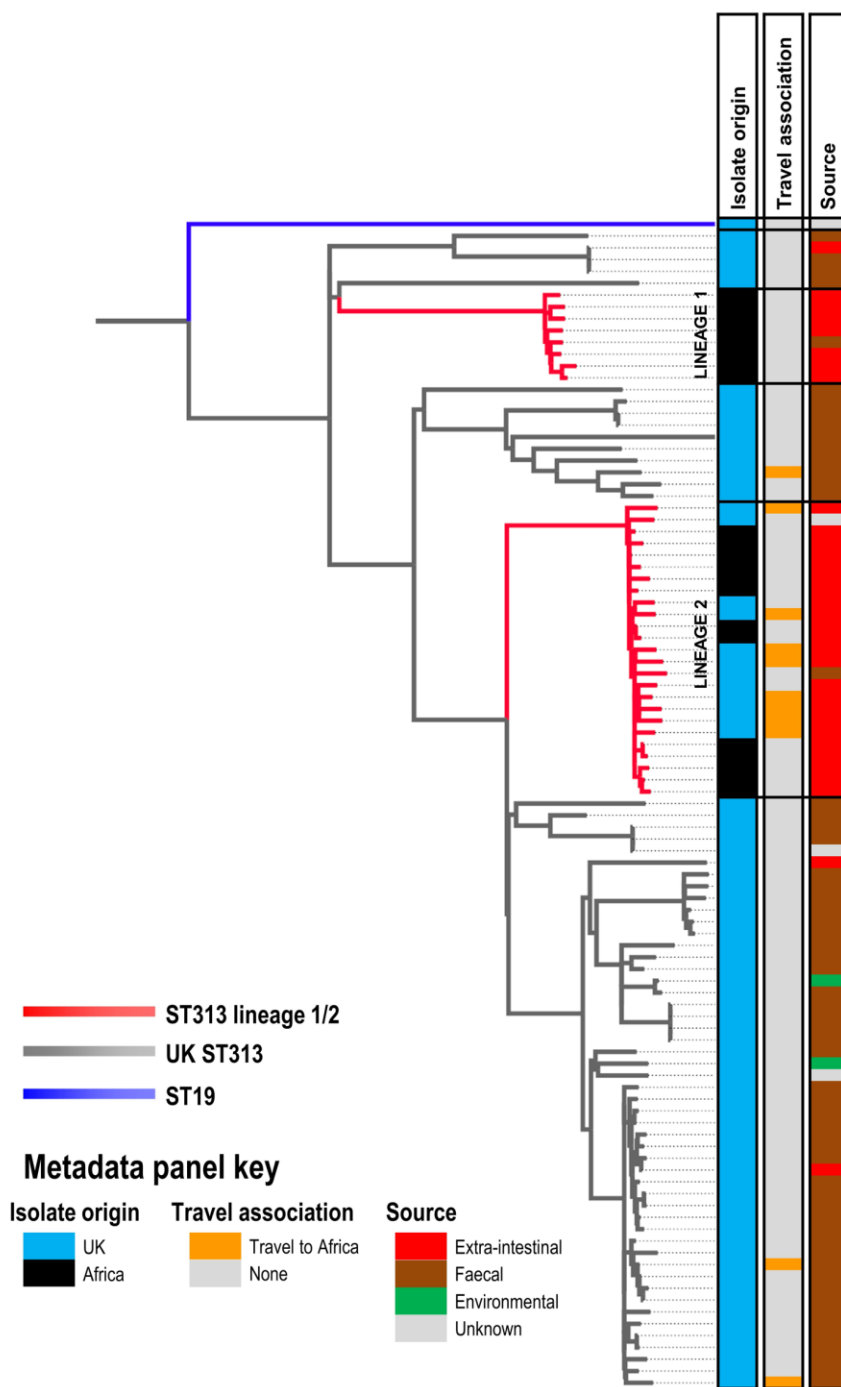
African S. Typhimurium is more invasive in chickens than global clades



ST313 not restricted to SAA



- 79/2,888 UK *S. Typhimurium* in PHE collection are ST313



Lineage I & II isolates associated INTS disease and travel to Africa

The remainder isolated from stool, prophage diversity, drug susceptible



Satheesh Nair



Public Health
England

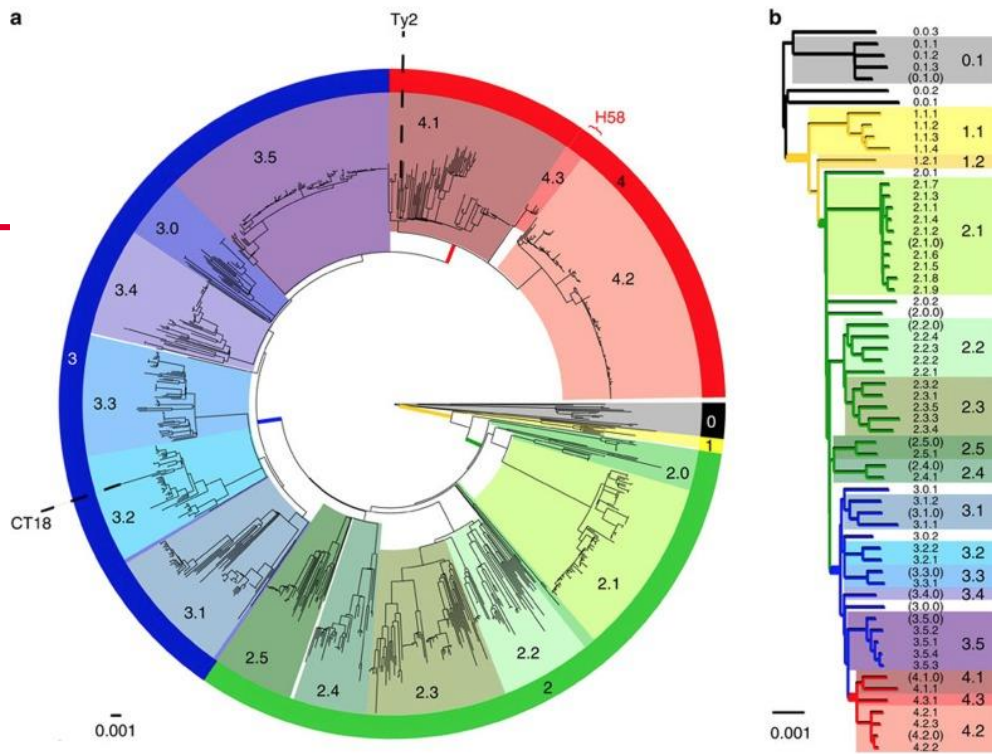
African clades of *S. Enteritidis*

- Genomic degradation
- Novel Prophage repertoire
- MDR cassette in virulence plasmid
- **Novel clades have highly conserved accessory genomes**

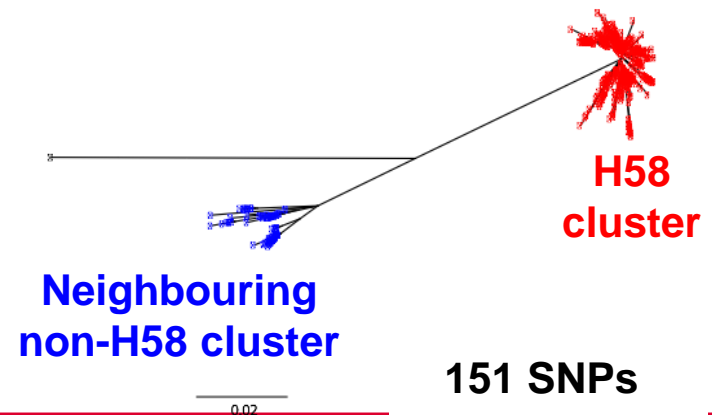
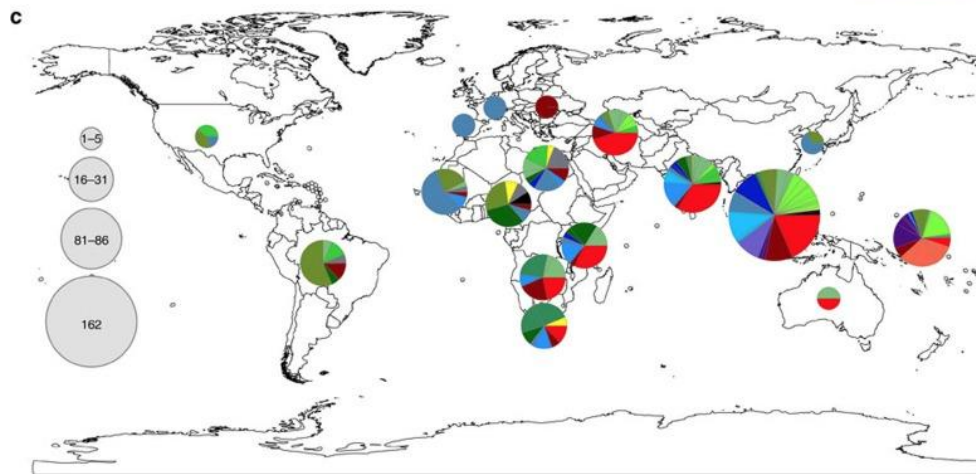




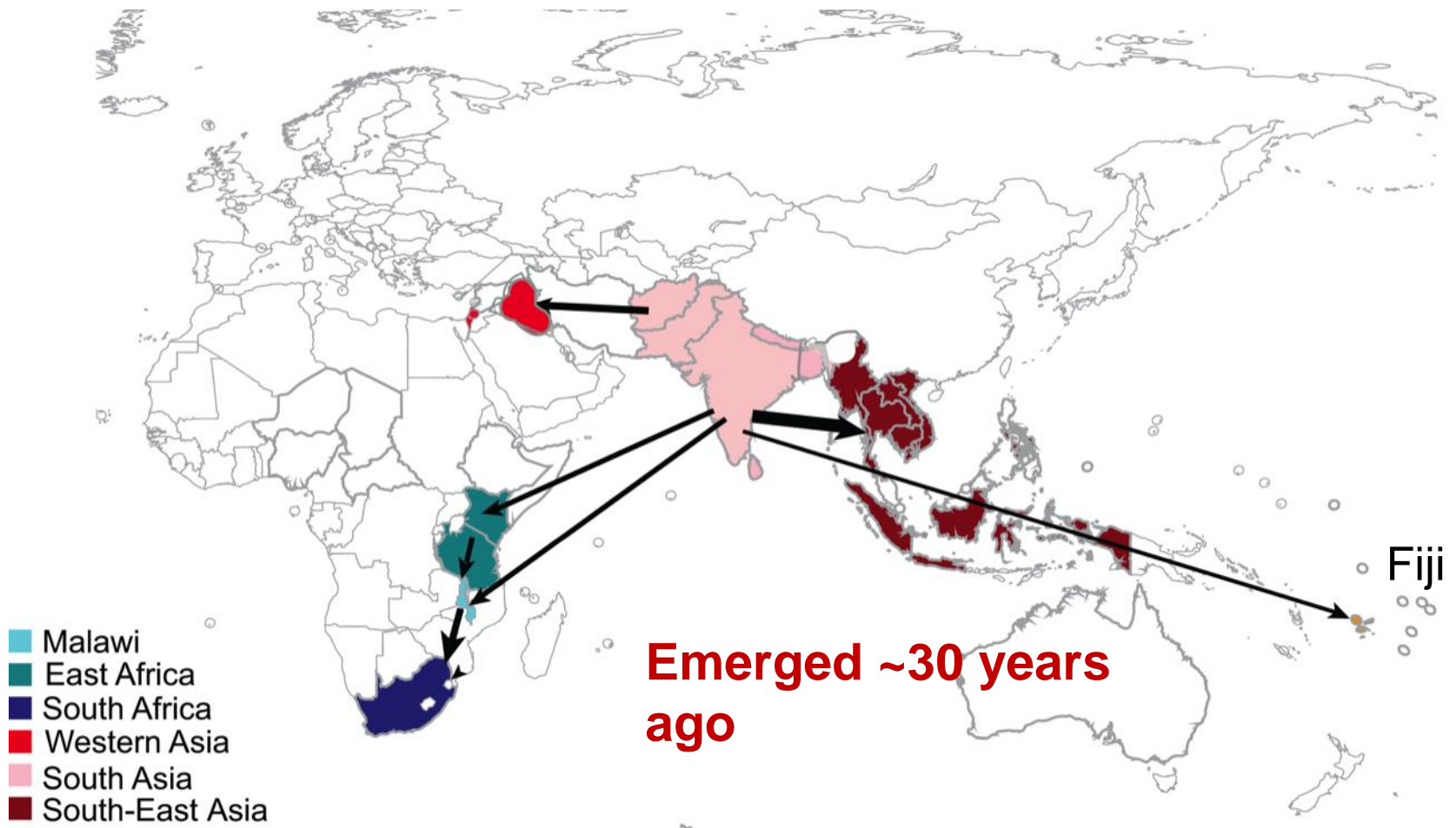
Placed in context of PHE collection (~3,000 isolates), there is restriction to SSA



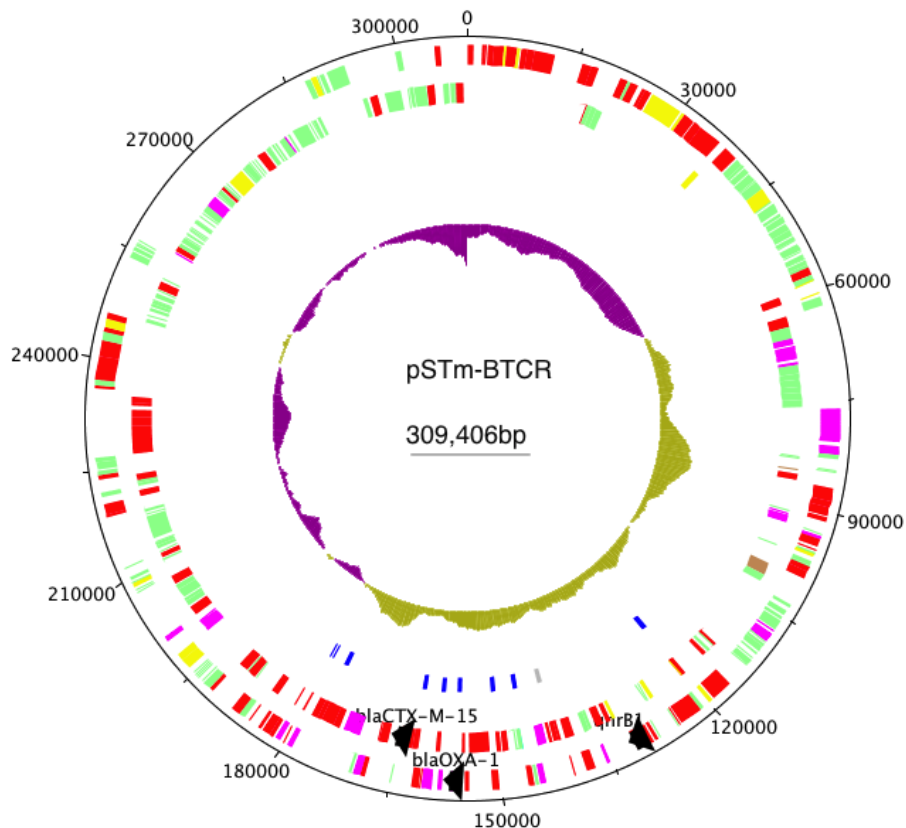
There's a novel clade of *S. Typhi* too!
Emergence of H58 lineage
(Or subclade 4.3.1)



Global dissemination of *S. Typhi* H58



Extended spectrum beta-lactamase producing variants an emerging problem in invasive Salmonella disease



- **bla_{CTX-M15} first reported in *S. Typhimurium* in Malawi**
- **Same plasmid subsequently reported in Kenya**
- **57% in rural west Kenya**
- **Emerging problem in *S. Typhi***
- **Has potential to make invasive *Salmonella* disease untreatable in many settings**

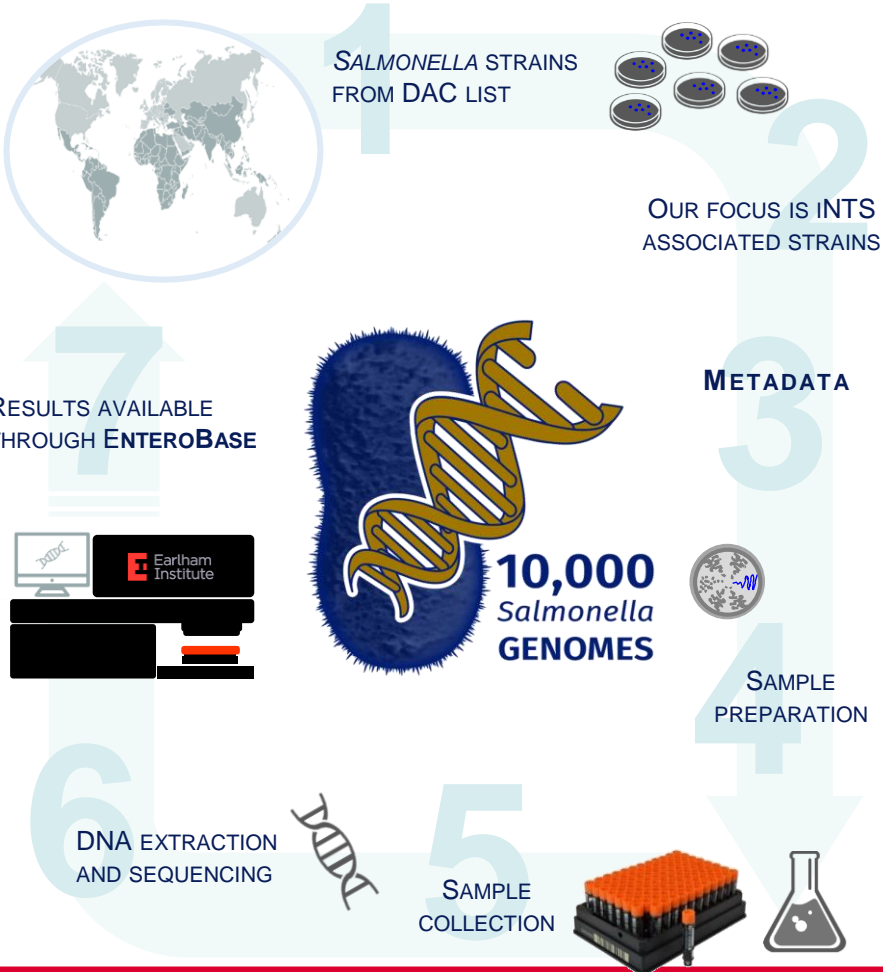
- **Novel clades of MDR S. Typhimurium and S. Enteritidis are exploiting the high prevalence of immunosuppressive conditions to cause epidemics of iNTS disease**
 - More invasive?
 - Less invasive?
 - Niche adaptation to particular environmental reservoir?
- **MDR H58 S. Typhi has established itself globally**
- **Drug resistance a major and evolving problem**
- **ESBL particularly frightening**

10,000 Salmonella genome project:



Aim: to understand the epidemiology, transmission & virulence of iNTS disease associated Salmonellae

HintonLab



Acknowledgements



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Sharon Tennant
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Vanessa Wong**