The genomic epidemiology of typhoidal and invasive nontyphoidal *Salmonella* in sub-Saharan Africa

Se Eun Park

Kellogg College

University of Oxford

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Abstract

Invasive salmonellosis is one of the most common community-acquired bloodstream infections among children and immunocompromised adults in sub-Saharan Africa. Clean water, improved sanitation and hygiene, which are essential for disease prevention and control, remain limited in most resource constrained countries. Typhoid fever and invasive nontyphoidal *Salmonella* (iNTS) disease have historically been managed by antimicrobial therapy. Ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (co-trimoxazole) served as the first choice of drugs for many years, but antimicrobial resistance (AMR)/multi-drug resistance (MDR) in these pathogens have emerged and spread inter-/intra-continentally. In this thesis, I conducted genomic, phylogenetic, and epidemiological analyses of invasive salmonellosis in Africa. My analysis supported existing hypotheses regarding the association between iNTS disease and *plasmodium falciparum* malaria in sub-Saharan Africa. Regarding the MDR typhoid fever, I found geographically distinct MDR *S.* Typhi lineages circulating in West (genotype 3.1.1) and East (genotype 4.3.1) Africa with high MDR incidence rates (>100/100,000 person-years observation) among children under 15 years old, particularly in Burkina Faso, Ghana and Kenya. iNTS disease was predominantly

caused by *S.* Typhimurium ST313 and *S.* Enteritidis ST11, which circulate across the African continent and were largely MDR. High MDR incidences (>100/100,000 PYO) of iNTS disease was found in children less than five years old across multiple countries; namely Burkina Faso, Ghana, and Guinea Bissau. Reduced susceptibility to fluoroquinolones was found in both *S.* Typhi (genotype 4.3.1 in East Africa; Kenya/Uganda) and iNTS (*S.* Enteritidis ST11 and *S.* Typhimurium ST313 in West Africa; Ghana). Third generation cephalosporin resistant *S.* Typhimurium ST313 was found in Kenya; a novel resistance-virulence IncI1 plasmid associated with *S.* Enteritidis ST11 isolates was also identified in Ghana, Senegal and Burkina Faso. Further, I conducted genomic analyses of NTS organisms isolated from stool samples of individuals living in selected communities in sub-Saharan Africa (Guinea-Bissau/Senegal). These data revealed a highly diverse collection of NTS serovars/sequence types, evidence of household transmission events, and found an *S.* Enteritidis ST11 isolate carrying IncF virulence plasmid in Senegal. These studies demonstrate the importance of continued disease surveillance combined with genomics to better understand the epidemiological landscape of invasive salmonellosis in Africa.

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Declaration

I, Se Eun Park, confirm that the work presented in this thesis is my own and was conducted at the Oxford University Clinical Research Unit in Ho Chi Minh City (OUCRU-HCMC), Vietnam and the International Vaccine Institute, Seoul, Republic of Korea. The data were collected through my work at the International Vaccine Institute as key research personnel of the study in collaboration with site partners in sub-Saharan Africa. The data analysed for this thesis involved partnership with the Wellcome Trust Sanger Institute for the whole genome sequencing of collected Isolates. I conducted the phylogeography and genomic analyses under the supervision and training at the OUCRU-HCMC (Professor Stephan Baker and Dr. Duy Thanh Pham), and further collaboration with the University of Melbourne (Professor Kathryn Holt, Dr. Zoe Dyson, and Dr. Sebastian Duchene) for the Bayesian analysis presented in Figure 4.6b in Chapter 4. Where data from other sources were used, I confirm that this has been indicated in the thesis. This thesis has not been submitted for a degree or other qualification to this or any other university.

“I am the Alpha and the Omega, the First and the Last, the Beginning and the End. Blessed are those who wash their robes, that they may have the right to the tree of life and may go through the gates into the city.”

Revelation 22:13-14

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Abbreviations

AAN	Asante Akim North district
AHRI	Armauer Hansen Research Institute
AIDS	Acquired Immuno-Deficiency Syndrome
AMR	Antimicrobial resistance
API	Analytical profile index
BF	Burkina Faso
BHP	Bandim Health Project
bp	Base pairs
CaT	Coalition against Typhoid
CC	Clonal complex
CDC	Centers for Disease Control and Prevention
CFU	Colony Forming Unit
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CO	Carbon monoxide
Co-trimoxazole	Trimethoprim-Sulfamethoxazole
DNA	Deoxyribose nucleic acid
DRC	Democratic Republic of Congo
ESBL	Extended Spectrum Beta Lactamase
ET	Ethiopia
EWM	East Wad Medani
GB	Guinea-Bissau
GDB	Global Burden of Disease
g/dL	Grams per decilitre (measurement of haemoglobin levels)
GEE	Generalized estimating equation
GH	Ghana
GPS	Global Positioning System
GTR	General Time Reversible
H	Hospital
H58	Haplotype 58
Hb	Haemoglobin
HC	Health Centre
HCF	Healthcare Facility
HDSS	Health and Demographic Surveillance System
HIV	Human Immunodeficiency Viruses
HO-1	Heme oxygenase 1
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IncHI1	Plasmids of HI1 incompatibility group

INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health in developing countries
iNTS	Invasive nontyphoidal *Salmonella*
IP	Institute Pasteur
IPD	Inpatient department
IVI	International Vaccine Institute
Kb	Kilobase (thousand base pairs)
KCCR	Kumasi Centre for Collaboration Research in Tropical Medicine
KCMC	Kilimanjaro Christian Medical Centre/Duke Collaboration
KEMRI	Kenya Medical Research Institute
km^2	Square kilometre
KY	Kenya
LMICs	Low-middle income countries
LPS	Lipopolysaccharide
LSD	Least-squares dating
MDR	Multidrug resistant
MG	Madagascar
MIC	Minimum Inhibitory Concentration
ML phylogenetic tree	Maximum likelihood phylogenetic tree
MLST	Multilocus sequence typing
MR	Moshi Rural
MRCA	Most recent common ancestor
MSRV	Semisolid Modification of RV medium
MU	Moshi Urban
µg	Microgram
µl	Microliter
µm	Micromole
mL (ml)	Millilitre
mm	Millimetre
NICD	National Institute for Communicable Diseases in South Africa
NTS	Nontyphoidal *Salmonella*
OPD	Outpatient department
OR	Odds Ratio
P	P-value
PCR	Polymerase Chain Reaction
PFGE	Pulsed-field gel electrophoresis
PMS	Polymorphonuclear leukocytes
PST	Plasmid sequence type
PYO	Person-years of observation
P. falciparum	*Plasmodium falciparum*
P. malariae	*Plasmodium malariae*
P. ovale	*Plasmodium ovale*
QRDR	Quinolone resistance-determining region
r	Spearman correlation coefficient

RDT	Rapid diagnostic test
ROS	Reactive oxidative species
RV	Rappaport-Vassilliadis
SA	South Africa
SD	Standard deviation
Ser83Phe	Serine to phenylalanine at codon 83
Ser83Tyr	Serine to tyrosine at codon 83
SNP	Single Nucleotide Polymorphism
SPI	Salmonella Pathogenicity Island
ST	Sequence Type
S. Agona	*Salmonella enterica* subsp. *enterica* serovar Agona
S. Chester	*Salmonella enterica* subsp. *enterica* serovar Chester
S. Choleraesui	*Salmonella enterica* subsp. *enterica* serovar Choleraesui
S. Corvallis	*Salmonella enterica* subsp. *enterica* serovar Corvallis
S. Dublin	*Salmonella enterica* subsp. *enterica* serovar Dublin
S. Durban	*Salmonella enterica* subsp. *enterica* serovar Durban
S. enterica	*Salmonella enterica* subsp. *enterica*
S. Enteritidis	*Salmonella enterica* subsp. *enterica* serovar Enteritidis
S. Give	*Salmonella enterica* subsp. *enterica* serovar Give
S. Hadar	*Salmonella enterica* subsp. *enterica* serovar Hadar
S. Johannesburg	*Salmonella enterica* subsp. *enterica* serovar Johannesburg
S. Muenster	*Salmonella enterica* subsp. *enterica* serovar Muenster
S. Paratyphi	*Salmonella enterica* subsp. *enterica* serovar Paratyphi
S. Poona	*Salmonella enterica* subsp. *enterica* serovar Poona
S. Stanleyville	*Salmonella enterica* subsp. *enterica* serovar Stanleyville
S. Typhi	*Salmonella enterica* subsp. *enterica* serovar Typhi
S. Typhimurium	*Salmonella enterica* subsp. *enterica* serovar Typhimurium
S. Virchow	*Salmonella enterica* subsp. *enterica* serovar Virchow
TCV	Typhoid conjugate vaccine
TSAP	Typhoid Fever Surveillance in Africa Program
UOA	University of Antananarivo
UOG	University of Gezira
UO	University of Ouagadougou
WGS	Whole genome sequencing
WHO	World Health Organization
XDR	Extensively drug-resistant

Chapter 1 Introduction

1.1 The genus *Salmonella*

The genus *Salmonella* are a collection of potentially pathogenic bacteria that belong to the family *Enterobacteriaceae* that can be typically isolated from soil, water, plants, and can constitute a component of the normal microbiota of animals (Terry C. Covert and Mark C. Meckes 2006). Salmonellae are typically aerobic, 2-5 µm long, 0.8-1.5 µm wide, non-spore-forming, Gram-negative bacilli that move with the use of peritrichous flagella (except for *Salmonella enterica* subsp. *enterica* serovars *pullorum* and *gallinarum*), and produce acid and gas (Ellermeier and Slauch 2006).

1.1.1 The microbiological identification of *Salmonella*

Various methods can be used to isolate *Salmonella* spp. from a range of sources. For the isolation of salmonellae from food and the environment, various selective enrichments are commonly used, including tetrathionate broth, selenite cystine broth, Rappaport-Vassilliadis (RV) medium, or a semisolid modification of RV medium (MSRV), which enrich for *Salmonella* and *Shigella* (Ellermeier and Slauch 2006). Selenite broth is commonly used to enrich *Salmonella* as it inhibits growth of most coliforms but has limited effects on *Salmonella*. The resulting organisms can then be plated on selective and differential media for further identification. Numerous selective plating media are used to isolate *Salmonella*, such as green phenol red agar or bismuth sulfite agar, which varies from high to low selectivity, respectively. Salmonellae grow readily on selective differential media, forming 2-3mm diameter colonies in 24-48 hours under temperature condition ranging from 10 to 43^{o}C (optimal temperature for growth being 37 ^{o}C) (Terry C. Covert and Mark C. Meckes 2006). Elevated incubation temperature may improve

the isolation of the salmonellae as it suppresses background growth, but may also suppress growth of some serovars, such as *S.* Typhi (Terry C. Covert and Mark C. Meckes 2006). For the isolation of *Salmonella* from clinical samples, nonselective media such as blood agar, or selective and differential media such as MacConkey or a highly selective medium, such as bismuth sulfite agar can be used. Upon isolation of salmonellae on selective media, presumptive *Salmonella* isolates can be further screened with triple sugar iron agar, urea broth, lysine iron agar, followed by biochemical and serological methods with commercial polyvalent O group, H, and Vi antisera.

1.1.2 *Salmonella* serology

Some features of the *Salmonella* cell exhibit unique biological structures and can aid pathogenicity. The cell envelope in Gram-negative bacteria, such as *Salmonella*, comprises a cell wall, an inner cell membrane, and an outer membrane (Figure 1.1). The cell wall contains peptidoglycan (poly-*N*-acetylglucosamine and *N*-acetylmuramic acid), which serves to maintain shape and determines cell rigidity. The cell structure of *Salmonella*, like other Gram-negative bacteria, contains a thin peptidoglycan layer adjacent to the (inner) cytoplasmic membrane (also known as cell membrane or plasma membrane) and additional outer membrane composed of phospholipids and lipopolysaccharides which separate the cell interior from the external environment. The glycosylation structure of the outer membrane lipopolysaccharide (LPS) is typically exclusive to specific bacterial serovars and aids in distinguishing sub-species and antigenic variation.

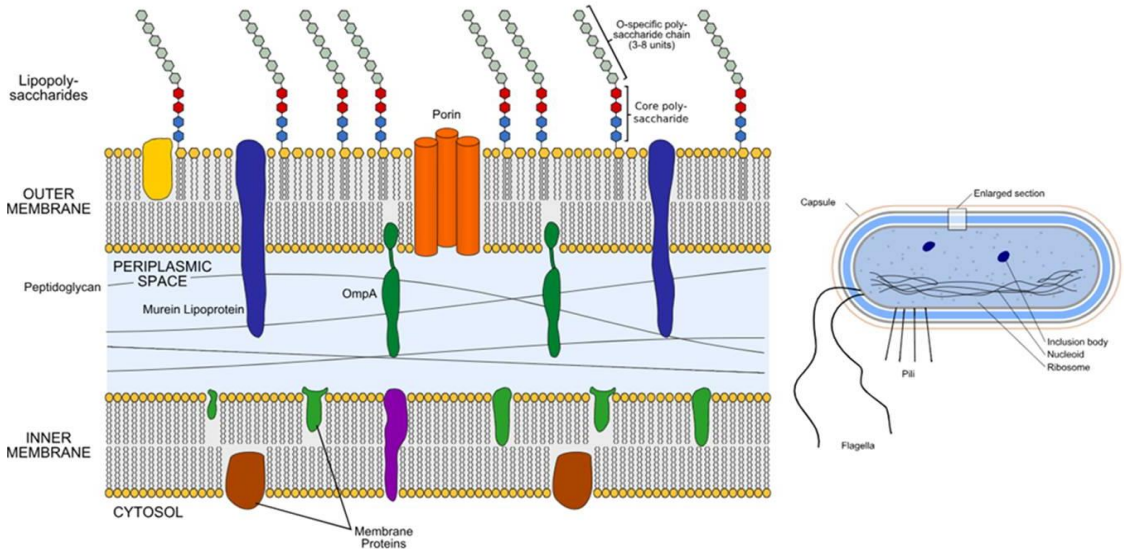


Figure 1.1 The structure of the outer membrane of a Gram-negative bacterium

Reproduced from drawings by Jeff Dahl. Gram-negative bacterium cell structure comprised of a cell wall, an inner cell membrane, and an outer membrane. A thin peptidoglycan layer is between the inner and additional outer membranes of Gram-negative bacteria, separating the cell interior from the external environment. Outer membrane LPS determines sub-species and antigenic variation.

LPS is composed of lipid A, core oligosaccharide, and a polymer of O-antigen sub-units (Christian R. H. Raetz and Chris Whitfield 2002). LPS has a significant role in the interaction between the bacterium and its host, particularly in case of pathogenic bacteria such as invasive *Salmonella*, which stimulate the immune system during infection. Lipid A is the predominant cause of the endotoxic effects of LPS. The O antigen, a polysaccharide polymerized from O subunits (each subunit comprised of four to six sugars), is the outermost component of the LPS in the outer membrane of *Salmonella*, and remains as the most immunodominant portion of the molecule (Ellermeier and Slauch 2006). *Salmonella* has variable O antigen structure with different monosaccharide components or linkages between monosaccharides or other modifications such as acetylation; changes in O antigen structure effect antibody recognition (Kim and Slauch 1999).

The genus *Salmonella* has over 2,500 serovars according to the Kauffmann-White antigenic scheme (Terry C. Covert and Mark C. Meckes 2006). Upon biochemical confirmation of *Salmonella*, serovars can be identified based on the antigenic structure (antibody agglutination reactions of the bacterial surface structures): O or somatic antigen (heat stable), H or flagella antigen (heat labile), and Vi antigen (capsule, possessed by only a few serovars) (Ellermeier and Slauch 2006). H antigen may occur in two forms, called phase 1 and phase 2 (Giannella 1996), commonly regulated coordinately to have one flagellar antigen expressed at any time (Herrera-León *et al.* 2004).

Kauffman-White scheme currently recognizes O antigen factors 1-67, which comprise approximately 50 different O antigen groups in *Salmonella*, of which serogroups A-E4

are largely associated with human infections (Ellermeier and Slauch 2006). The O antigen groups and antigenic formulas of the *Salmonella* serovars associated with humans and animal infections are summarized in Table 1.1.

Table 1.1 The antigenic formulas of representative *Salmonella* serovars typically associated with human and animal infections and diseases

Representative serovars	Serogroup	Antigenic formulas		
		O antigen	H phase 1	H phase 2
S. Typhi (host restricted to human)	O:9 (D1)	9, 12, [Vi]	d	-
S. Paratyphi A (host restricted to human)	O:2 (A)	[1], 2, 12	a	[1, 5]
S. Paratyphi B (host restricted to human)	O:4 (B)	[1], 4, [5], 12	b	1, 2
S. Paratyphi C (host restricted to human)	O:7 (C1)	6, 7, [Vi]	c	1, 5
S. Typhimurium (host generalised)	O:4 (B)	[1], 4, [5], 12	i	1, 2
S. Enteritidis (host generalised)	O:9 (D1)	[1], 9, 12	g, m	-
S. Dublin (host adapted to cattle; though can cause infections in humans and other animals)	O:9 (D1)	1, 9, 12, [Vi]	g, p	-
S. Choleraesuis (host adapted to pig; though can cause infections in other animals)	O:7 (C1)	6, 7	c	1, 5
S. Gallinarum (host restricted to chicken)	O:9 (D1)	[1], 9, 12	-	-

Reproduced based on Kauffman-White scheme in J. P. Euzeby (SBSV) & B. Barrett (Indiana State Department of Health).

The majority of *Salmonella* serovars are motile with flagella that are present on the bacterial surface. *Salmonella* subsp. I, II, IIIa and VI are capable of producing two (or three) functionally equivalent but immunologically distinct flagellar subunits (biphasic), and serological distinction in H antigens are also defined by the Kauffmann-White scheme (Phase 1, Phase 2) (Ellermeier and Slauch 2006).

The *Salmonella* serovars Typhi and Paratyphi C (and occasionally Dublin) have a capsular polysaccharide known as the Vi antigen. Vi-expression is encoded in *viaB* locus, which is comprised of at least 10 genes (*tviA-E* and *vexA-E*) and encodes the regulatory enzymes for the biosynthesis and export of antigen. The *viaB* locus is part of the genomic island SPI7 (*Salmonella* Pathogenicity Island 7), which is a 134 kb cluster of virulence-associated genes in the *S.* Typhi chromosome (Christian R. H. Raetz and Chris Whitfield 2002). The Vi antigen is associated with bacterial resistance to innate immune responses (phagocytosis), and inhibits early inflammatory responses from human intestinal epithelial cells and monocytes following infection with *S.* Typhi (Looney and Steigbigel 1986; Sharma and Qadri 2004).

1.1.3 Salmonellae nomenclature

Historically, the classification and nomenclature of *Salmonella* was based on the diseases caused (e.g., *S.* Typhi causing human typhoid) or source (e.g., *S.* Typhimurium causing typhoid-like disease in mice), or location of isolation (e.g., *S.* Newport). Biochemical classification followed to distinguish species or groups or genera (4th edition of Bergey's Manual), and was subsequently improved with the introduction of serologic methods (agglutination tests) to further define serologic types (6th edition of Bergey's Manual; F. Kauffmann and P. R.Edwards 1952). However, *Salmonella*

serovars that had been identified in the earlier years were sometimes classified as species (e.g., *S.* bovismobificans), and several nomenclature systems were inconsistently used to define species, subspecies, subgenera, groups, subgroups, and serovars, causing confusions and inconsistency in communications among scientists, and health workers (Brenner *et al.* 2000).

Suggestions on improvements for *Salmonella* nomenclature have evolved over time with the development of biotechnology. In the 1960s, the one serovar-one species concept, based on the serologic identification of O (somatic) and H (flagellar) antigens, was proposed by Kauffmann (Fritz Kauffmann 1966), whereby each serovar became a separate species (e.g., *S. paratyphi A, S. enteritidis*). However, this would have translated into over 2,500 species of *Salmonella* today. In the 1970s, Crosa *et al.* found that typical *Salmonella* were 85-100% identical at the molecular level (e.g. DNA-DNA hybridization tested polynucleotide sequence relatedness among all serovars and subgenera I, II, and IV of *Salmonella* and all serovars of *Arizona*) meaning these serovars were related at the species level and thus belonged to a single species (Crosa *et al.* 1973).

In the 1980s, Le Minor and Popoff proposed the term *S. enterica* to classify the type species for *Salmonella*, which was adopted by Center for Disease Control and Prevention (CDC) in 1986, though was denied by the Judicial Commission that commented that this may result in undermining of the status of *Salmonella* serovar Typhi (e.g. *S. enterica* subsp. *enterica* serovar Typhi, which may be overlooked by physicians) (Brenner *et al.* 2000; Euzeby 1999). Le Minor and Popoff further suggested the seven subgenera of *Salmonella* be classified as subspecies (e.g. subspecies I, II, IIIa,

IIIb, IV, V, and VI). In the late 1980s, Reeves *et al*. proposed a new species, *Salmonella bongori*, which was an elevation from the formerly classified *Salmonella choleraesuis* subsp. *bongori* (subspecies V), based on findings that *Salmonella* subgroup V is highly divergent from the other subgroups (e.g. 43% DNA relatedness of subgroup V to the other subgroups of *Salmonella*) (Reeves *et al.* 1989).

Currently, the *Salmonella* nomenclature recommended by the World Health Organization Collaborating Centre and the CDC is broadly used and classifies the genus *Salmonella* into two species: *Salmonella enterica* and *Salmonella bongori* (formerly subspecies V). *Salmonella enterica* is comprised of six subspecies: I (*S. enterica* subsp. *enterica*), II (*S. enterica* subsp. *salamae*), IIIa (*S. enterica* subsp. *arizonae*), IIIb (*S. enterica* subsp. *diarizonae*), IV (*S. enterica* subsp. *houtenae*), and VI (*S. enterica* subsp. *indica*) (Table 1.2) (Grimont and Weil 2007; Tindall *et al.* 2005). Among these subspecies, *S. enterica* subsp. I (*S. enterica* subsp. *enterica*) constitute 59% of the total 2,463 *Salmonella* serovars, and O-antigen serogroups A, B, C1, C2, D and E within subsp. I cause 99% of *Salmonella* infections in humans and warm-blooded animals. *S. bongori* is typically found in cold-blooded animals and environment (Brenner *et al.* 2000; Grimont and Weil 2007).

Table 1.2 *Salmonella* nomenclature in use at CDC, 2000

Genus	Species	Subspecies (subsp.)	Note
Salmonella	*enterica*	Subsp. *enterica* (I) Subsp. *salamae* (II) Subsp. *arizonae* (IIIa) Subsp. *diarizonae* (IIIb) Subsp. *houtenae* (IV) Subsp. *indica* (VI)	*Salmonella enterica* subsp. *enterica* (I) includes typhoidal and (invasive) nontyphoidal *Salmonella* serovars
	bongori	(formerly subsp. V)	

Reproduced based on Farmer *et al*., 1984 in Brenner F. W. *et al*. (2000).

1.1.4 The ecology of *Salmonella*

Salmonella can inhabit the environment and the gastrointestinal tract of animals. Like many Gram negative bacteria, the survival of *Salmonella* in the environment, such as aquatic ecosystems, is influenced by various factors including protozoa, antibiosis, organic matter, algal toxins, dissolved nutrients, ultraviolet light, heavy metals, and temperature (Terry C. Covert and Mark C. Meckes 2006). Enteric pathogens in aquatic environments can also be viable but non-culturable. Salmonellae can often be isolated from polluted (1 to 1,100/100 mL from non-disinfected wastewater effluents) and high-nutrient waters (Terry C. Covert and Mark C. Meckes 2006). However, the 'natural' primary habitat of *Salmonella* is the gastrointestinal tract of animals (Table 1.3). To survive in these habitat, *Salmonella* must strategize to persist in a commensal manner in some hosts, or live in environmental reservoirs and transmit from host to host (Ellermeier and Slauch 2006).

Table 1.3 Typical habitats of *Salmonella* species and subspecies

***Salmonella* species and subspecies**	**No. of serovars**	**Habitat**
S. enterica subsp. *enterica* (I)	1,454	Warm-blooded animals
S. enterica subsp. *salamae* (II)	489	Cold-blooded animals and environment
S. enterica subsp. *arizonae* (IIIa)	94	
S. enterica subsp. *diarizonae* (IIIb)	324	
S. enterica subsp. *houtenae* (IV)	70	
S. enterica subsp. *indica* (VI)	12	
S. bongori (formerly subsp. V)	20	
Total	2,463	

Reproduced based on the Kauffmann-White scheme described in Brenner F. W. *et al.* (2000).

The host adaptability of *S. enterica* subsp. *enterica* serovars is highly variable across the serovars and can be broadly divided into three categories: (1) host adapted (primarily infecting one host but capable of causing disease in others), (2) host restricted (known to infect only a single host), (3) host generalised (capable of infecting various animals though the course of disease may differ in different hosts) (Ellermeier and Slauch 2006; Uzzau *et al.* 2000). Some of the most common serovars of *S. enterica* subsp. *enterica* causing infection and disease in human and animals are summarized in Figure 1.2 and Table 1.4.

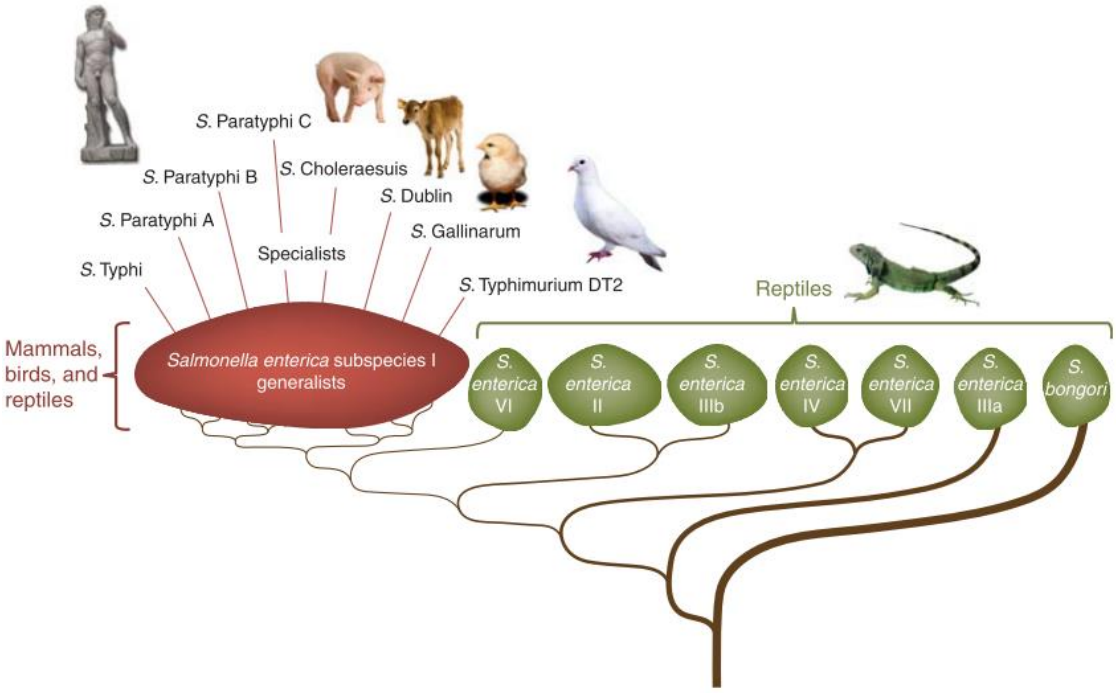


Figure 1.2 The host range of various members of the genus *Salmonella*

Reproduced from Bäumler and Fang (2013). Original legend: "The genus *Salmonella* consists of two species, *S. enterica* and *S. bongori*. *S. enterica* is further subdivided into seven subspecies, designated I, II, IIIa, IIIb, IV, VI, and VII. Serovars of *S. bongori* and *S. enterica* subspecies II, IIIa, IIIb, IV, VI, and VII are largely reptile associated and can be occasionally transmitted from this reservoir to humans. The majority of serovars belonging to *S. enterica* subspecies I are generalists that have reservoirs in mammalian, avian, and reptilian species. Specialists with a more restricted host range have independently evolved from this group several times."

Table 1.4 The host range of selected *Salmonella enterica* subsp. *enterica* serovars

Representative Serovars	Host range classification	Natural hosts	Rare hosts
S. Typhi	Host restricted	Humans	-
S. Paratyphi A	Host restricted	Humans	-
S. Paratyphi B	Host restricted	Humans	-
S. Paratyphi C	Host restricted	Humans	-
S. Typhimurium	Host generalised	Humans, poultry, swine, bovines, and rodents	None
S. Enteritidis	Host generalised	Humans, poultry, and rodents	Swine and bovines
S. Dublin	Host adapted	Bovines	Humans and bovines
S. Choleraesuis	Host adapted	Swine	Humans
S. Gallinarum	Host restricted	Poultry	None

Reproduced based on Ellermeier C. D. and Slauch J. M. citing Uzzau et al. (2000) and Edwards *et al*. (2002).

1.1.5 The diagnosis of invasive Salmonellosis

The predominant diagnostic approaches for confirming invasive *Salmonella* infections include culture-based method, molecular approaches (Polymerase Chain Reaction (PCR)), and serologic testing. Among these methods, bacterial culture followed by microbiological identification remains the gold standard for diagnosis due to its relatively higher sensitivity (approximately 50-80% for blood culture) (Crump *et al.* 2015), despite potential issues surrounding the sensitivity and time-/resource-intensive nature the process (Andrews and Ryan 2015).

The positivity rates of culture-based methods are highly variable and dependent on several different factors (Crump *et al.* 2015; Andrews and Ryan 2015). These factors include: (1) Antimicrobial pre-treatment patients; blood culture positivity rate is typically 80% in untreated enteric fever patients, this may be as low as 40% in pre-treated patients. (2) Sample types; there are higher bacterial concentrations in bone marrow resulting in higher sensitivity from bone marrow aspirates even after antimicrobial pre-treatment and irrespective of the duration of disease prior to sample collection, bone marrow may be more applicable for severe and complicated disease. The median concentration of bacteria is roughly ten times higher in bone marrow (median value of 9 CFU/mL) than blood (Wain *et al.* 2001). Cerebrospinal fluid (CSF) may only be positive in younger children with nontyphoidal *Salmonella* (NTS) meningitis (Naicker *et al.* 2016). *Salmonella enterica* can be cultured from feces in up to 30% of typhoid fever patients and <1% of urine samples. (3) Volume of samples; in acute typhoid fever, the median concentration of bacteria is 1 colony-forming unit (CFU) per mL of blood (two-thirds of which are intracellular) (Wain *et al.* 1998). The sensitivity of faecal culture increases from 10% to 30% through multiple sample testing;

feces samples have a greater sensitivity than rectal swabs. (4) The timing of sample collection; the optimum period for detecting organisms circulating in the bloodstream is in the first or second week of illness. (5) Types of enrichment and culture media; Selenite F enrichment and selective media increases culture sensitivity (Crump *et al.* 2015).

The optimum procedure for blood culture diagnosis is approximately 10-15 ml or 2-4 ml of blood from adults and children (children often have higher level of bacteremia than adults) prior to antimicrobial therapy. Children <15 years of age exhibit higher median blood bacterial counts of *S.* Typhi than adults (1.5 verses 0.6 CFU/mL respectively) (Wain *et al.* 1998). The optimum ratio of blood volume to culture broth is 1:10 (e.g. 5 ml blood in 45 ml broth or per commercial blood culture system), which is inoculated immediately into a blood culture bottle and incubated at 37^{o}C. Inoculated culture bottles are screened for turbidity, gas formation, and other evidence of growth after 1day and up to 7 days. Bottles with signs of positive growth are sub-cultured on Blood Agar, Chocolate Agar, and MacConkey Agar. Culture plates are incubated at 37^{o}C for 18-24 hours in an aerobic incubator, and if growth is observed, colony morphology is noted. Positive cultures are normally evident within 48 hours, and mostly positive by five days (Andrews and Ryan 2015). Subsequently, subculture, biochemical testing (e.g. API-20E (bioMerieux, Inc.) or BBL Enterotube II (BD) or Vitek), and agglutination tests with specific antisera are performed to identify *Salmonella* serovars (Ellermeier and Slauch 2006).

PCR (conventional and real-time PCR) have been developed to detect *S.* Typhi and *S.* Paratyphi A in blood, but the sensitivity remains limited due to the low number of

bacteria circulating in the blood (Nga *et al.* 2010). The first serological method for typhoid fever was developed in 1896 (Felix-Widal test), which detects agglutinating antibodies against LPS (O) and flagellar (H) antigens of *S.* Typhi. The Widal test uses serum samples of suspected typhoid fever patients during the acute and convalescent phases, 10 days apart, whereby a 4-fold increase in antibody titre determines the test positive result. However, there are limitations associated with this test: (1) patients often have high antibody titres upon infection before the onset of clinical symptoms, which challenges the test positive definition (4-fold rise from initial and subsequent samples); and (2) a high false positive rate due to cross-reacting epitopes with other Enterobacteriaceae. New rapid serologic tests have been developed and commercially available (Typhidot, Tubex TF, Life-Assay, Multi-Test Dip-S-Ticks, Mega-Salmonella, SD Bioline Typhoid rapid test, and Enterocheck-WB; all use a comparable method of detecting specific IgM and IgG antibodies against *S.* Typhi), but these still lack sensitivity and specificity due to antigen cross-reactivity and antibody levels of background population (Crump *et al.* 2015). Further, both PCR and serological approaches are limited for detection of invasive nontyphoidal *Salmonella* in Africa. Studies in West Africa and Vietnam suggested the PCR is not sensitive enough to be used as a rapid diagnostic test without pre-test enrichment culture (Gordon 2012).

1.2 The pathogenesis of invasive *Salmonella*

Within *S. enterica*, specific serovars can cause disease in humans or animals, which includes gastroenteritis, enteric fever, and septicemia. Serovars with varying host adaptability are associated with different host-pathogen interaction and virulence. Typically, evidence shows that the more host-specific serovars, such as serovar *S.* Typhi, are more virulent in humans and able to breach host defense mechanisms. These

infection pathways result in higher mortality (10-32% in typhoid perforation cases) (Parry *et al.* 2002) and greater disease severity, in comparison to pathogens that lack host specificity such as *S. enterica* subsp. *enterica* serovar Typhimurium (*S.* Typhimurium) and *S. enterica* subsp. *enterica* serovar Enteritidis (*S.* Enteritidis). These organisms are more associated with disease in young people, who do not have mature immune system, or calves with *S.* Typhimurium infection (Table 1.5). Another current hypothesis is that vertebrate pathogens that have a higher mortality rate do not fully adapt to their hosts in order to safeguard their habitat by exhibiting less virulence (Bäumler *et al.* 1998). However, this theory does not explain the strongly host-adapted *S.* Typhi that causes typhoid fever in humans, which has a 12-32% mortality rate, and *S.* Typhimurium or *S.* Enteritidis, zoonotic *Salmonella* serovars that cause gastroenteritidis in humans with <0.5% mortality in developed countries. Furthermore, the hypothesis of host-specificity conferring more virulence and mortality is not true for NTS in Africa. A more recent systematic review of the invasive NTS (iNTS) disease in Africa during 1966 and 2014 exhibited high case fatality rates in immunocompromised children and adults, with varying ranges from <12% (parts of Kenya, Mozambique, etc.) to around 20-50% (largely among hospitalised HIV patients in parts of Zambia, Malawi, Democratic Republic of Congo, Zimbabwe, Liberia, Cote d'Ivoire, etc.), and up to 60-73% (among hospitalised children with clinical septicaemia in Northern Tanzania, and mostly HIV infected with bacteraemia upon hospitalisation, Nairobi, urban Kenya) (Uche, MacLennan and Saul 2017). An in-depth research on host adaptation of *Salmonella* serovars, using a theoretical model with the basic case reproductive number (R_0) and the ability of a *Salmonella* serovar to persist in a host population, suggests the selective pressure inflicted by host immune response on pathogen populations that may result in a natural balance. For example, a zoonotic *S. enteritidis* in poultry, causing

human infections and diseases, may have found its ecological niche upon elimination of avian-adapted *S. gallinarum* (O9-antigen, serogroup D1) in the 1970s (loss of flock immunity against immunodominant O-antigen) (Kingsley and Bäumler 2000). More research on the mechanisms of host adaptation and persistence of *Salmonella* serovars is needed.

Table 1.5 Diseases caused by *Salmonella* subspecies I serovars

Hosts	Representative *S. enterica* subspecies I serovar(s)	Disease	Symptoms or sign(s)	Susceptible age groups
Humans	Typhi	Typhoid fever	Septicemia, fever	Children and adults
	Paratyphi A, B, C	Paratyphoid fever	Septicemia, fever	Children and adults
	Typhimurium	Gastroenteritidis	Diarrhea, dysentery, fever	Children (<4-5 year)
	Enteritidis	Gastroenteritidis	Diarrhea, dysentery, fever	Children (<4-5 year)
Cattle	Typhimurium	Salmonellosis	Diarrhea, dysentery, septicemia, fever	Calves (<8 weeks)
	Dublin	Salmonellosis	Diarrhea, dysentery, septicemia, fever abortion	Calves and adult cattle
Poultry	Gallinarum	Fowl typhoid	Diarrhea, comb discoloration, septicemia	Growing stock and adults
	Pullorum	Pullorum disease	Diarrhea, septicemia	Newly hatched birds
Pigs	Choleraesuis	Pig paratyphoid	Skin discoloration, septicemia, fever	Weaned and adult pigs
	Typhimurium	Salmonellosis	Diarrhea	Weaned pigs (<4 months)
	Typhisuis	Chronic paratyphoid	Intermittent diarrhea	-
Sheep	Abortusovis	Salmonellosis	Septicemia, abortion, vaginal discharge	Adult sheep
			Diarrhea, dysentery, septicemia	Lambs
	Typhimurium	Salmonellosis	Diarrhea, dysentery, septicemia	Lambs
Horses	Abortusequi	Salmonellosis	Septicemia, abortion	Adult horses
			Diarrhea, septicemia	Foals
	Typhimurium	Salmonellosis	Diarrhea, septicemia	Foals
Wild rodents	Typhimurium	Murine typhoid	Septicemia, fever	-
	Enteritidis	Murine typhoid	Septicemia, fever	-

Reproduced based on Baumler A. J. *et al*. (1998).

1.2.1 Typhoid fever

Enteric fever is a combined generic term for the disease caused by *S.* Typhi (typhoid fever) and *S.* Paratyphi A, B, and C (paratyphoid fever). *S.* Typhi is transmitted fecal-orally, often via contaminated food or water. After ingestion, the organisms survive the gastric acid (increased pH reduces the infectious dose, but salmonellae have an adaptive acid-tolerance response that allow their survival in the low gastric pH) (Haraga, Ohlson and Miller 2008) and reach the small intestine. Upon entering the small intestine, salmonellae cross the intestinal mucous layer and avoid killing by digestive enzymes, bile salts, secretory IgA, antimicrobial peptides and other innate immune defenses, which allows them to gain access to the underlying epithelium (Haraga, Ohlson and Miller 2008).

Salmonellae use multiple mechanisms to cross the intestinal barrier: (1) bacterial-mediated endocytosis; invading non-phagocytic enterocytes of the intestinal epithelium by disrupting epithelial border using fimbrial adhesins and being engulfed by membrane ruffles, causing intestinal inflammation and diarrhea. (2) Entering microfold cells (M cells) in the Peyer's patches; which are organised lymphoid follicles that are part of gut associated lymphoid tissue. The Peyer's patches are located in the lowest segment of the small intestine and surveil the gastrointestinal system for foreign objects. (3) Translocation through intestinal epithelia after uptake by CD18-expressing phagocytes, which enable salmonellae to cross the intestinal barrier without active interaction with the epithelial surface (Haraga, Ohlson and Miller 2008). *S.* Typhi then enter intestinal macrophages by inducing micropinocytosis, releasing virulence mechanisms to survive and replicate within macrophages. The organism further disseminate through mesenteric lymph nodes, reaching liver, spleen, bone marrow

where they can survive and multiply (Figure 1.3) (Baker, Favorov and Dougan 2010; Kaur and Jain 2012; de Jong *et al.* 2012).

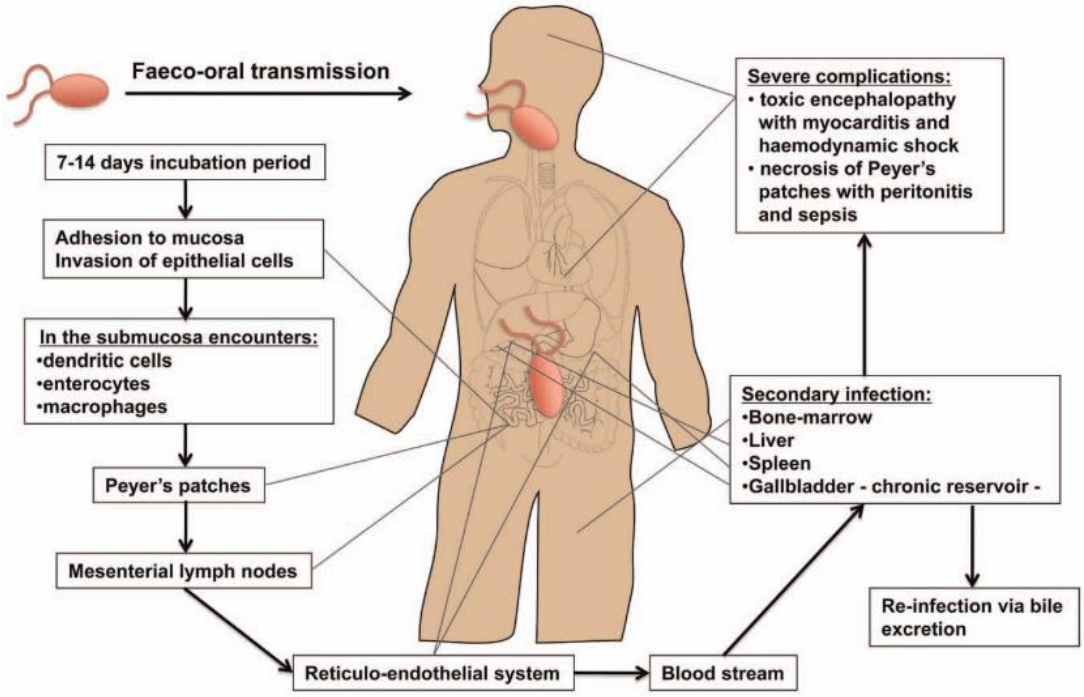


Figure 1.3 Dissemination of *S.* Typhi during systemic infection

Reproduced from de Jong *et al.* (2012) Original legend: "Typhoid is usually contracted by ingestion of food or water contaminated by fecal or urinary carriers excreting *S.* Typhi. The incubation period is usually 7 to 14 d. In the small intestine the bacteria adhere to the mucosa and then invade the epithelial cells. The Peyer's patches, which are aggregrated lymphoid nodules of the terminal ileum, play an important role in the transport to the underlying lymphoid tissue. Specialized epithelial cells such as M cells overlying these Peyer's patches are probably the site of internalization of *S.* Typhi. Once the bacteria have penetrated the mucosal barrier, the invading organism translocates to the intestinal lymphoid follicles and the draining mesenteric lymph nodes, and some pass on to the reticuloendothelial cells of the liver and spleen. During the bacteremic phase, the bacteria are widely disseminated throughout the body. Secondary infection can occur with liver, spleen, bone-marrow, gallbladder, and Peyer's patches as the most preferred sites. The gallbladder is the main reservoir during a chronic infection with *S.* Typhi and invasion occurs either directly from the blood or by retrograde spread from the bile. Of interest, the ability of *Salmonella* to form biofilms on gallstones is likely to be a critical factor in establishment of chronic carriage and shedding of *S.* Typhi (Crawford *et al.* 2010). The bacteria that are excreted in the bile can then reinvade the intestinal wall by the mechanism previously described or are excreted by feces. Typical clinical symptoms are fever, malaise, and abdominal discomfort. Clinical features such as a tender abdomen, hepatomegaly, splenomegaly, and a relative bradycardia are common. Rose spots, the classical skin lesions associated with typhoid fever, are relatively uncommon and occur in 5%-30% of cases. The most severe manifestations of typhoid leading to sepsis and death are either necrosis of the Peyer's patches resulting in gut perforation and peritonitis or a toxic encephalopathy associated with myocarditis and haemodynamic shock (Parry *et al.* 2002; Everest *et al.* 2001)."

After an incubation period of 7-14 days, the bacteria are released back into bloodstream (bacteremia) and patients experience the onset of clinical symptoms. The symptoms of enterica fever include sustained fever and occasionally diarrhea, abdominal pain, and may involve liver, spleen, respiratory, and neurological complications. Symptoms typically start 1-3 days after exposure and may persist for 2-3 weeks if untreated or treatment fails. Reportedly 1-4% of individuals infected with *S.* Typhi may become chronic carriage (Ellermeier and Slauch 2006). Patients that excrete *S.* Typhi in feces have higher bacteremias than those who do not (median of 3 verses 1 CFU/mL), and the concentration of bacteria in the blood negatively correlates with duration of illness but positively correlates MDR organisms (1.3 MDR vs 0.5 susceptible CFU/mL) (Wain *et al.* 1998). The concentration ratio of bacteria in the bone marrow compared to the blood increases as the illness progresses (Wain *et al.* 2001). Severe clinical complications associated with typhoid fever include gastrointestinal bleeding (10% of patients) (Parry *et al.* 2002), intestinal perforation (3% of patients with mortality rate of nearly 40%) (van Basten and Stockenbrügger 1994), encephalopathy, osteomyelitis, and abscesses in the liver, spleen, kidneys and other organs (Table 1.6) (Huang and Dupont 2005).

Table 1.6 The complications of typhoid fever

Typhoid Fever Complications	
Abdominal	Gastrointestinal perforation Gastrointestinal haemorrhage Hepatitis Cholecystitis (usually subclinical)
Cardiovascular	Asymptomatic electrocardiographic changes Myocarditis Shock
Neuropsychiatric	Encephalopathy Delirium Psychotic states Meningitis Impairment of coordination
Respiratory	Bronchitis Pneumonia (*S.* Typhi, *Streptococcus pneumoniae*)
Hematologic	Anaemia Disseminated intravascular coagulation (usually subclinical)
Other	Focal abscess Pharyngitis Miscarriage Relapse Chronic carriage

Reproduced from C. Parry *et al.* (2002).

1.2.2 Invasive nontyphoidal Salmonella (iNTS) disease

Nontyphoidal *Salmonella* are transmitted through oral ingestion of contaminated food (meat, poultry, raw milk, eggs, and egg products) or water, but exposure to particular animals that carry bacteria can increase the risk of infection (Bush and Perez 2018). A distinguishable pathologic feature of nontyphoidal *Salmonella* disease compared to typhoid fever is the early innate inflammatory response in the intestine, which results in the infiltration of polymorphonuclear leukocytes (PMNs) into the intestinal lumens (Haraga, Ohlson and Miller 2008). The PMN chemokine interleukin (IL)-8 and cytotoxic granules released by PMNs result in the destruction of the intestinal mucosa, contributing to inflammatory diarrhea (Bush and Perez 2018). The early mucosal inflammatory response is a typical feature of nontyphoidal *Salmonell*a and is distinct from *S.* Typhi disease (Figure 1.4) (Dougan and Baker 2014).

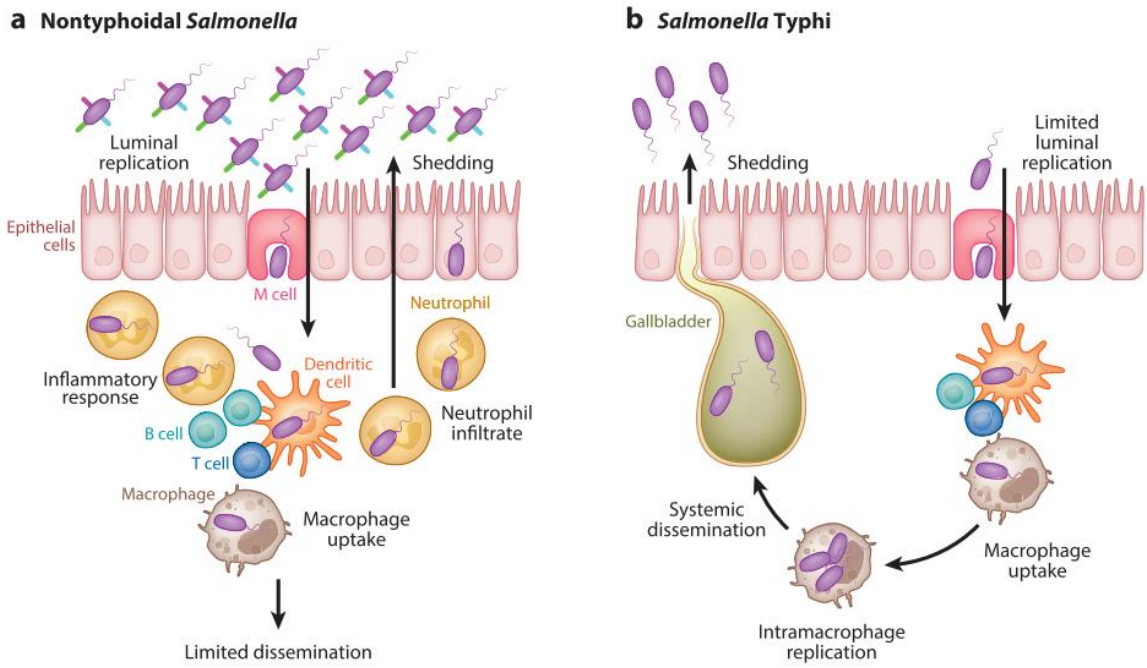


Figure 1.4 Typhoidal and nontyphoidal *Salmonella* infections

Reproduced from Dougan and Baker (2014). Original legend: "A generalized comparison of infection associated with (*a*) gastroenteritis (nontyphoidal *Salmonella*) and (*b*) typhoid (*S.* Typhi). The multicolored fingers for nontyphoidal bacteria represent a repertoire of adhesion molecules. Nontyphoidal strains may consequently have more options in terms of their route of infection with humans. Vi expression and other factors such as modified regulation of gene expression and effector repertoire may influence mucosal inflammatory responses to *S.* Typhi."

Upon ingestion of nontyphoidal *Salmonella*, similar to *S.* Typhi, the bacteria invade epithelial cells and survive in macrophages. This evokes acute intestinal inflammation that results in gastroenteritidis within 24 hours of ingestion, causing diarrhea, while neutrophils of host cells attempt to kill the bacteria in the intestinal lumen (Bäumler and Fang 2013). The bacterial pathogen is cleared from intestinal tissues as the adaptive host immune response takes place, and fecal shedding of bacteria subsides in a few weeks (Bäumler and Fang 2013), though limited data suggests up to 5% of patients may develop bacteraemia (Hohmann 2001).

In comparison to the NTS gastroenteritidis, iNTS disease may be a result of several inherited immunodeficiencies such as chronic granulomatous disease (phagocytes unable to destroy ingested organisms) (Lazarus and Neu 1975), sickle-cell disease (macrophage dysfunction), and B-cell deficiencies (Leen *et al.* 1986), and malaria (MacLennan *et al.* 2008) (Table 1.7) (Ao *et al.* 2015; Park *et al.* 2016; Morpeth, Ramadhani and Crump 2009). Paediatric patients with inherited deficiencies of interleukin (IL)-12 and IL-23 cytokines may be also related to high incidence of recurrent iNTS infections (Maclennan *et al.* 2004). Intracellular persistence and recrudescence of iNTS bacteria is suggested to explain the recurrent iNTS bacteremia in HIV-infected adults, detected in both blood and bone marrow (Gordon 2012; Gordon *et al.* 2010).

Such host susceptibility to iNTS is also investigated in relations to the genetic basis of inheritable or/and inter-individual variations, providing further insights into human immunity to invasive *Salmonella* in twofold: primary immune-deficiencies and population-based levels more recently using genome-wide association study (GWAS)

(Gilchrist, MaClennan and Hill 2015). An assessment of the host genetic determinants of invasive *Salmonella* disease demonstrated the role of innate and adaptive immune mechanisms. For example: the first GWAS of invasive *Salmonella* disease identified the role of acquired immunity to the MHC class II antigen in controlling intracellular *Salmonella*; and T_H17 cell-mediated neutrophils and oxidative burst capacity in controlling extracellular bacteria (Gilchrist, MaClennan and Hill 2015).

The association between NTS bacteremia and malaria is also a major public health concern in many malaria endemic sub-Saharan African countries, particularly when the common clinical symptom of iNTS disease and malaria are fever, making the clinical diagnosis and treatment decision difficult. Host defense mechanisms and pathogenesis of iNTS and malaria co-infection remains complex. A case series of six Malawian children with iNTS (*S.* Typhimurium) and concomitant malaria infection in early 2006 further suggested an increased disease severity and case fatality associated with this coinfection (Cunnington *et al.* 2011; MacLennan 2012). Subsequently, a mice model suggested that the induction of HO-1 in response to malaria infection is responsible for increased susceptibility to NTS (Figure 1.5) (Cunnington *et al.* 2011; MacLennan 2012). Another mouse model suggested that the *Plasmodium falciparum* parasites induce IL-10, resulting in the impairment of phagocytic cells and consequently decreased inflammatory pathology and increased systemic bacterial colonization (Lokken *et al.* 2014).

Other animal studies of rhesus macaques also exhibited a simian immunodeficiency virus (SIV) infection resulting in the depletion of T helper type 17 (T_H17) CD4 T cells in ileal mucosa, impairing mucosal immune response preventing systemic

dissemination of *S*. Typhimurium from the gastrointestinal tract (Raffatellu *et al.* 2008; Dandekar, George and Bäumler 2010). However, further research is warranted to better understand the intracellular pathogenesis of iNTS disease and the transmission mechanisms of iNTS associated organisms.

Table 1.7 Risk factors associated with complex pathogenesis of iNTS disease

Younger age group and malnutrition	Younger children have relative gastric achlorhydria compared to adults, which may contribute to increased risk to iNTS disease (as reduced gastric acidity is associated with increased risk of gastrointestinal infection) (Morpeth, Ramadhani and Crump 2009). However, infants (1-4 months) may be protected by maternal antibodies (IgG) or/and exclusive breast-feeding that provides colostrum and also reduces the risk to exposure to unsafe water and food (Morpeth, Ramadhani and Crump 2009; MacLennan *et al.* 2008; Brent *et al.* 2006).
Malaria (and anaemia)	Limited understanding on the mechanism associated with malaria and iNTS. Existing literature suggest malarial hemolysis impairs macrophage and neutrophil function (due to accumulated malarial pigments of phagocytic cells, saturation of iron-binding proteins, increased iron availability to NTS). Some studies compared an association between recent (but not current) malaria or malarial anaemia and NTS, compared to other bacteremia (Morpeth, Ramadhani and Crump 2009; Brent *et al.* 2006; Enwere *et al.* 2006; Berkley *et al.* 2005).
HIV	iNTS is found more common among HIV-infected individuals (with low CD4 lymphocyte counts) (Gordon *et al.* 2010; Brent *et al.* 2006; Berkley *et al.* 2005; Chien-Ching Hung *et al.* 2007; MacLennan *et al.* 2017).
Prior antimicrobial use	Prior exposure to antimicrobials contribute to abnormal gastrointestinal flora, which may be compromise the mucosal immune response (Morpeth, Ramadhani and Crump 2009).
Sickle cell disease	Sickle cell disease is associated with higher risk for bacterial sepsis including iNTS bacteremia (Morpeth, Ramadhani and Crump 2009; Ebong 1986).

Organised based on relevant literatures referenced in this table.

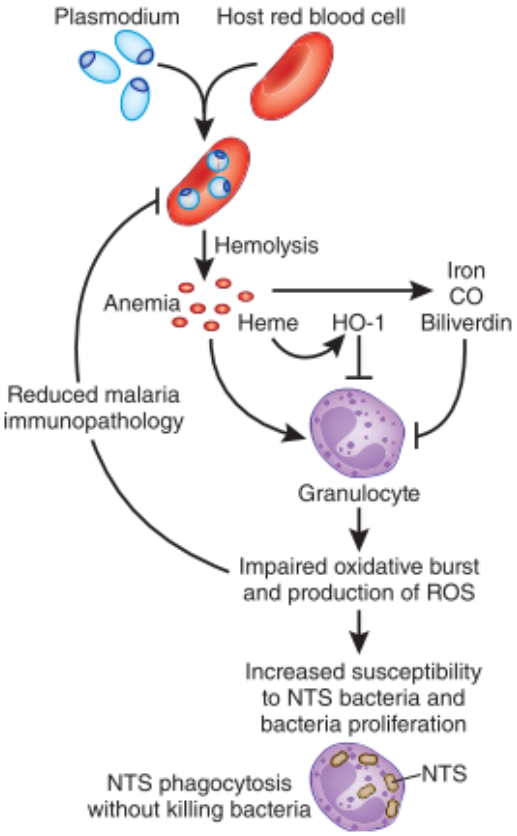


Figure 1.5 Host defenses against malaria favour *Salmonella* infections

Reproduced from MacLennan (2012). Original legend: "Opposing consequences of inhibiting oxidative burst function through induction of HO-1 during malaria and NTS co-infection. After malaria infection, hemolysis of infected red blood cells results in anaemia and the release of the pro-oxidant, heme. Free heme, in turn, induces HO-1 expression in granulocytes and granulocyte precursors in the bone marrow that mobilize to the main bloodstream; HO-1 catabolizes heme to iron, carbon monoxide (CO) and biliverdin. Whereas heme causes immunopathology in malaria with cell death through production of reactive oxidative species (ROS) and apoptosis, HO-1 reduces this immunopathology through both the removal of heme and the effects of the heme-derived metabolites. However, HO-1 also increases the susceptibility to NTS infection. NTS proliferation is established in immature and mature granulocytes, which are able to phagocytose *S. typhimurium* but cannot efficiently kill owing to suppressed oxidative burst function mediated by HO-1 and heme catabolites."

1.3 The epidemiology of *Salmonella* disease

1.3.1 Typhoid fever

The global disease burden of typhoid and paratyphoid fever study analysed data from 22 eligible studies and estimated approximately 21.7 million typhoid fever cases with 217,000 fatalities and 5.4 million paratyphoid fever cases during 2000 (Crump, Luby and Mintz 2004). Regions with a high incidence of typhoid fever included: South-Central Asia and Southeast Asia (>100/100,000 cases/year); rest of Asia, Africa, Latin America and Caribbean, and Oceania. Europe, North America, and the rest of the developed world had a low incidence of <10/100,000 cases/year (Crump, Luby and Mintz 2004). The more recent Global Burden of Disease 2017 (GDB 2017) study estimated 14.3 million cases of typhoid and paratyphoid fevers globally in 2017 (with a global case fatality of 0.95%, 135,900 deaths) (Figure 1.6), suggesting a decline from 25.9 million in 1990 and 21.7 million in 2000 (Stanaway *et al.* 2019). However, *S.* Typhi was still estimated to cause over 76% of enteric fever cases globally in 2017 (Stanaway *et al.* 2019).

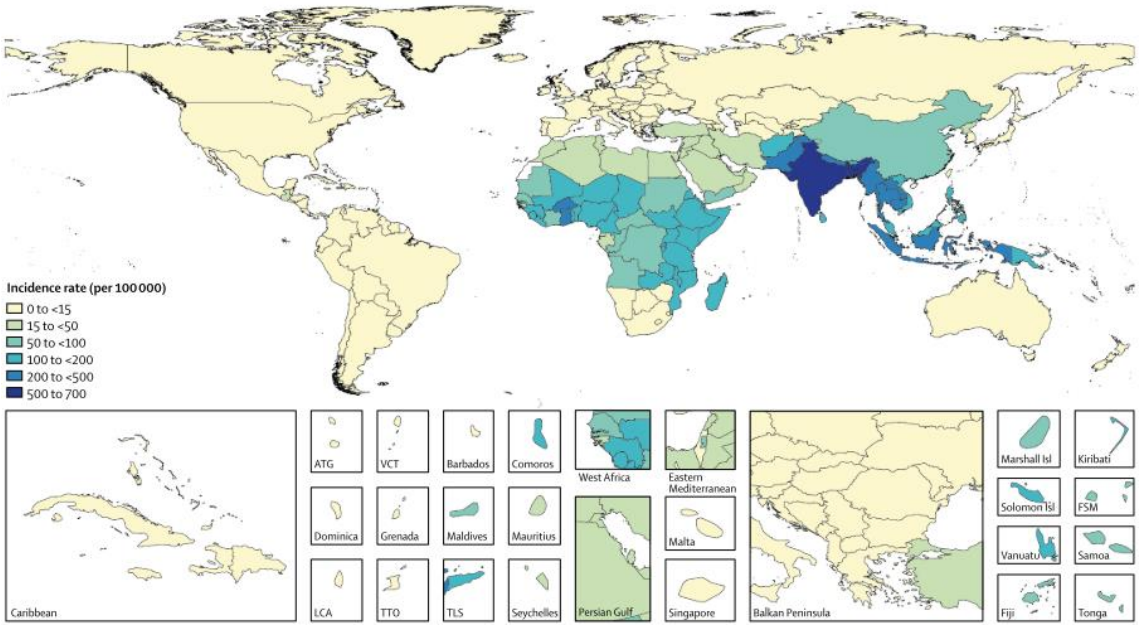


Figure 1.6 The incidence rates (per 100,000) of typhoid and paratyphoid fevers, by country, in 2017

Reproduced from Stanaway *et al.* (2019) including the GBD 2017 Typhoid and Paratyphoid Collaborators. Original legend: "Unfilled locations are those for which GBD does not produce estimates. The inset maps detail smaller locations. ATG=Antigua and Barbuda. FSM=Federated States of Micronesia. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. Isl=Islands. LCA=Saint Lucia. TLS=Timor-Leste. TTO=Trinidad and Tobago. VCT=Saint Vincent and the Grenadines."

Typhoid fever is thought to arise mainly in urban areas in low-middle income countries (LMICs) in South and Southeast Asia. In 2000, Africa was estimated to have a medium incidence (50 illnesses per 100,000 persons per year with a case fatality of 1%) based on limited data from few vaccine trials in Egypt and in South Africa conducted over a decade earlier (Crump and Heyderman 2015). However, more recent data have also shown a substantial burden of disease in urban and rural areas of sub-Saharan Africa with invasive salmonellosis (typhoid and iNTS) being one of the most common causes of community acquired bloodstream infections (Crump and Heyderman 2015; Morpeth, Ramadhani and Crump 2009). A multi-country typhoid fever surveillance project in sub-Saharan Africa conducted between 2010 and 2014 estimated adjusted incidence rates of typhoid fever ranging from 0 to 383 per 100,000 person-years of observation (PYO) (Marks *et al.* 2017). In comparison to a multi-country study in Asia (Diseases of the Most Impoverished programme (DOMI)), the burden of typhoid fever in these African countries was equivalent to or greater than incidences reported in the studied Asian countries in the early 2000s (Marks *et al.* 2017; Ochiai *et al.* 2008; Owais *et al.* 2010). Children aged 2-14 years old exhibited higher incidences of typhoid fever than those aged 15 years or older in the majority of surveillance sites in sub-Saharan Africa. Some earlier studies suggested a high burden of typhoid fever in urban settlements with high population densities in Africa, more recent studies also described a higher typhoid incidence in children living in rural areas (Marks *et al.* 2017; Pham Thanh *et al.* 2016). The regional incidence of typhoid fever were subject to seasonality and the duration of surveillance, indicating the importance of continued multi-year surveillance to better monitor the endemicity and localised outbreaks of typhoid fever.

1.3.2 Invasive nontyphoidal *Salmonella* disease (iNTS disease)

According to a 2010 worldwide study of the burden of nontyphoidal *Salmonella* (NTS) gastroenteritis, approximately 93.8 million cases of gastroenteritis due to NTS were estimated to occur globally each year. These infections resulted in 155,000 deaths, including 2.5 million cases of NTS gastroenteritis with 4,100 deaths per year in Africa (Majowicz *et al.* 2010). However, this may be an under-estimation of the burden of NTS gastroenteritis in Africa given the limitations of returning traveller data. A more recent study investigated the causes of diarrhoea in the Global Enteric Multicenter Study (GEMS) using quantitative real-time PCR (qPCR) of 11,400 stool samples from 5,700 cases and matched asymptomatic controls, and exhibited higher incidence estimates than original GEMS microbiological methods, though particularly for six most attributable pathogens including *Shigella* spp., rotavirus, adenovirus, ST-ETEC, *Cryptosporidium* spp., and *Campylobacter* spp., suggesting the use of molecular diagnostic methods may substantially increase attributable disease incidence at the population-level (Liu *et al.* 2016).

Typically a zoonotic pathogen associated with self-limiting diarrhea in humans, NTS has been increasingly reported as an invasive pathogen, causing systemic bloodstream infections in African children and immunocompromised adults (Morpeth, Ramadhani and Crump 2009). Studies suggest that NTS bacteremia has been reported consistently in tropical sub-Saharan Africa since the 1960s (Graham 2010; Vandenberg *et al.* 2010), but invasive nontyphoidal *Salmonella* (iNTS) was first acknowledged in Gambian children with malaria in 1987 (Feasey *et al.* 2012; Mabey, Brown and Greenwood 1987). The first case series of iNTS in acquired immuno-deficiency syndrome (AIDS) patients in Africa was from the Democratic Republic of Congo in 1983, and was

associated with a group B *Salmonella* (Piot *et al.* 1984). Additionally, AIDS patients with NTS bacteraemia was reported in the United States in 1984 (Profeta *et al.* 1985). The first epidemiological report on the relationship between invasive *Salmonella* infection and AIDS was made in New Jersey (Profeta *et al.* 1985). By the 1990s, NTS (particularly *S.* Typhimurium) had been identified as common non-opportunistic bacteria associated with morbidity and mortality in HIV-infected persons in sub-Saharan Africa (Gilks *et al.* 1990).

Each year there are approximately 3.4 million cases of iNTS disease globally, which have 681,000 fatalities (case fatality rate of ~20%) (Ao *et al.* 2015; Feasey *et al.* 2012). In Africa, an annual incidence of 175-388/100,000 iNTS disease cases have been estimated in children aged <5 years (Gordon 2012; Enwere *et al.* 2006; Berkley *et al.* 2005; Sigaúque *et al.* 2009), with a case fatality rate of around 24% (MacLennan *et al.* 2008). A more recent multicentre study across sub-Saharan Africa reported iNTS disease to be one of the major causes of bacteremia in febrile patients in Africa, exhibiting adjusted incidences ranging from 0 to 742 per 100,000 person-years in sampled locations (Marks *et al.* 2017). Among the various NTS serovars, serovars Typhimurium and Enteritidis are the most common cause of invasive NTS disease in sub-Saharan Africa (Gordon 2012). Compared to the low incidences of iNTS disease in Asia (7.2/100,000 among 2-15 year old children in Karachi, Pakistan and 1.8 and 1.0/100,000 in all age groups in Kolkata, India and Jakarta, Indonesia, respectively), the disease is significantly a public health concern in sub-Saharan Africa (Gordon 2012). A lower prevalence of *Plasmodium falciparum* malaria and HIV in Asia may explain this disparity between Asia and Africa, but further investigations are needed (Feasey *et al.* 2012).

Numerous recent studies further suggest the relationship between iNTS disease with malaria, HIV, anaemia, and malnutrition (MacLennan 2012; Gordon 2012; Berkley *et al.* 2009; Reddy, Shaw and Crump 2010). Severe malarial anaemia (Graham *et al.* 2000; Bronzan *et al.* 2007), recent malaria (Brent *et al.* 2006), acute severe malaria (Berkley *et al.* 2009), and sickle cell disease (Williams *et al.* 2009) all have positive correlation with iNTS disease in African children (Table 1.8). Several studies also suggest iNTS disease is seasonal in Africa (Gordon *et al.* 2008), whereby iNTS cases increase during the rainy season in parallel to the increased incidences of malaria in both children and adults (Feasey *et al.* 2012). Several studies reported that iNTS is more common than *S.* Typhi in malaria-endemic regions of Africa (Graham 2010; Reddy, Shaw and Crump 2010).

Notably, there is paucity of data on the NTS or/and iNTS carrier status. A study in Kenya found that 6.9% of human household contacts of paediatric iNTS index cases carried NTS in their stools (Kariuki *et al.* 2006). However, data are limited and more comprehensive research is required to better understand the epidemiology and transmission mechanisms of NTS and iNTS disease in Africa.

Table 1.8 Risk factors associated with iNTS disease in Africa (1996 to 2014)

Risk factor	Studies (Author, Year, Study location)	Measure of association reported (confidence interval); OR: Odds Ratio; RR: Risk Ratio	Comments
HIV infection	Malawi (Archibald *et al.* 2002)	OR: 4.4 (0.6-93)	P value not significant
	Kenya (Berkley *et al.* 2005)	OR: 3.21 (1.95-5.28)	OR adjusted for age, HIV infection and malnutrition
	Malawi (Bronzan *et al.* 2007)	OR: 11.6 (2.1-63.7) Adjusted OR: 22.1 (3.3-146)	Children with severe malarial anaemia
	Senegal (Seydi *et al.* 2005)	Prevalence: 81% vs 36%	P=0.00001, iNTS in patients with vs without HIV
	Kenya (Gilks *et al.* 1990)	OR: 48.2 (13-176)	*S.* Typhimurium only
	Tanzania (Blomberg *et al.* 2007)	Prevalence: 25% vs 8.4%	P=0.022; iNTS in HIV infected vs uninfected patients
	Malawi (Peters *et al.* 2004)	OR: 5.3 (1.2-2.2)	
Malnutrition	Kenya (Berkley *et al.* 2005)	OR: 1.68 (1.15-2.44)	OR adjusted for age, HIV infection and malnutrition
Severe (WAZ<-3)	Mozambique (Mandomando *et al.* 2009b)	OR: 1.44 (1.08-1.91)	P=0.004; iNTS vs Other bacteraemia; Multivariate
Wasting	Ghana (Nielsen *et al.* 2012)	OR: 1.9 (1.2-3.4)	
	Mozambique (Sigaúque *et al.* 2009)	OR: 2.42 (1.92-3.04)	Unadjusted analysis
Severe acute	Tanzania (Biggs *et al.* 2014)	OR: 2.01 (1.15-3.52)	P=0.014; Multivariate
Malaria			
P. falciparum	Mozambique (Mandomando *et al.* 2009b)	OR: 1.61 (0.91-1.47)	P=0.8; iNTS vs Other bacteraemia; Univariate
P. falciparum in children >6m	Malawi (Graham *et al.* 2000)	RR: 1.5 (1.2-2.2)	P<0.01; compared to other pathogens combined
Recent malaria	Biggs et al, 2014, Tanzania (Biggs *et al.* 2014)	OR: 4.13 (2.66-6.44)	P<0.001; Multivariate
Age			
12-23 months vs >5 yrs	Kenya (Berkley *et al.* 2005)	Prevalence: 23% vs 7%	P value (<0.001)
≥2 vs <2 yrs	Malawi (Bronzan *et al.* 2007)	OR: 4.3 (0.8-22.9) Adjusted OR: 9.6 (1.4-64.8)	Children with severe malarial anaemia
2-11 months	Mozambique (Mandomando *et al.* 2009b)	OR: 2.07 (1.07-4.01)	P=<0.001; iNTS vs Other bacteraemia; Multivariate
1-4 yrs	Mozambique (Mandomando *et al.* 2009b)	OR: 3.90 (2.06-7.40)	P=<0.001; iNTS vs Other bacteraemia; Multivariate
Anaemia			
Moderate	Mozambique (Mandomando *et al.* 2009b)	OR: 1.86 (1.34-2.58)	P=<0.001; iNTS vs Other bacteraemia; Multivariate
Severe	Mozambique (Mandomando *et al.* 2009b)	OR: 3.48 (2.03-5.95)	P=<0.001; iNTS vs Other bacteraemia; Multivariate
Severe	Malawi (Graham *et al.* 2000)	RR: 7.2 (3.4-15.3)	P<0.0001; compared to other pathogens combined
Sickle cell	Kenya (Williams *et al.* 2009)	OR: 35.6 (16.4-76.8)	Age adjusted (<14 years)
Anaemia (Hb<7)	Malawi (Peters *et al.* 2004)	OR: 2.2 (1.1-4.5)	
Severe	Tanzania (Biggs *et al.* 2014)	OR: 2.19 (1.48-3.23)	P<0.001; Multivariate
Setting/Rural	Tanzania (Biggs *et al.* 2014)	OR: 2.23 (1.25-3.96)	P=0.006; Univariate

Reproduced from Uche, MacLennan and Saul (2017). m: month. Yrs: years.

1.4 The treatment of invasive *Salmonella* disease and antimicrobial resistance

1.4.1 Antimicrobial resistance in typhoidal *Salmonella*

Antimicrobial therapy plays a major role in typhoid control and reducing mortality. Originally, penicillin, streptomycin, and the sulphonamides effectively cleared the infecting bacteria until resistance emerged (Spring 1975; Aminov 2010). Chloramphenicol was first used to treat typhoid fever in 1948 (Woodward *et al.* 1948; Wain *et al.* 2015). From this point chloramphenicol was considered the primary drug for typhoid, and it contributed to the reduction of mortality rate of typhoid fever from 12% to 1% (Woodward and Smadel 1964). However, chloramphenicol resistance was reported in individual *S.* Typhi isolates from the 1950 and chloramphenicol resistant *S.* Typhi had emerged by mid-1970s, (Anderson and Smith 1972; Murti, Rajyalakshmi and Bhaskaran 1962; Paniker and Vimala 1972) and was associated with epidemics in Mexico (Olarte and Galindo 1973), India (Anderson 1975), Vietnam (Butler *et al.* 1973), and South Korea (Chun *et al.* 1977). As a consequence, the use of ampicillin and trimethoprim-sulfamethoxazole (co-trimoxazole) increased in the 1960s and 1970s (Wain *et al.* 2015). However, *S.* Typhi exhibiting resistance to these alternative first-line drugs emerged towards the end of the 1980s and the early 1990s (Mirza, Beeching and Hart 1996) and were associated with numerous outbreaks of MDR *S.* Typhi in South Asia (Bangladesh (Rahman *et al.* 2006; Albert *et al.* 1991), India (Rathish, Chandrashekar and Nagesha 1994; Threlfall *et al.* 1992), Pakistan (Shanahan *et al.* 2000; Butt *et al.* 2005), and Nepal (Pokharel *et al.* 2006)), Southeast Asia (Vietnam (Connerton *et al.* 2000)), and Africa (Kenya (Kariuki *et al.* 2000) and South Africa (Coovadia *et al.* 1992)). Subsequently, MDR *S.* Typhi have been increasingly reported, including sub-Saharan Africa (Britto *et al.* 2018) and the phenotype is commonly associated with a transferable incompatibility group HI1 (IncHI1) plasmid (Wong *et al.*

2015). However, recent studies now report chromosome-mediated MDR *S.* Typhi isolates in parts of Asia, including Bangladesh, India, Pakistan, Malaysia, Kuwait (Mirza *et al.* 2000; Chiou *et al.* 2015), and Africa (Hendriksen *et al.* 2015).

The global emergence and spread of MDR *S.* Typhi led to the use of fluoroquinolones (ciprofloxacin, ofloxacin) as alternative drugs of choice for typhoid treatment in the 1980s and 1990s (Wain *et al.* 2015). This practice became more common in Asia (Rahman *et al.* 2006; Threlfall *et al.* 1999; Brown *et al.* 1996; Mehta, Randhawa and Mohapatra 2001; Wain *et al.* 1997). However, the extensive use of fluoroquinolones also resulted in increased resistance against ciprofloxacin with the first case of highly ciprofloxacin resistant *S.* Typhi reported from India in 2005 (MICs ranging from 0.125-1 µg/ml to >32 µg/ml) (Renuka *et al.* 2005). An increased incidence of ciprofloxacin resistant *S.* Typhi have been recorded in South Asia and travellers to this region (Karkey, Thwaites and Baker 2018; Koirala *et al.* 2012; Menezes *et al.* 2012; Lee *et al.* 2013; García-Fernández *et al.* 2015; Harish *et al.* 2008; Ahmed *et al.* 2006; Dutta *et al.* 2008). Fluoroquinolone resistance in *S.* Typhi is associated with resistance genes (*qnrS1, qnrB, aac(6')-Ib-cr*) and chromosome-mediated fluoroquinolone resistance exhibited mutations in various chromosomal genes including *gyrA* (often at codon 83 or/and codon 87) (Brown *et al.* 1996; Renuka *et al.* 2005; Chau *et al.* 2007; Saha *et al.* 2006), *gyrB, parC* (typically at codon 80) (Gaind *et al.* 2006) and *parE*. Countries where MDR and fluoroquinolone (ciprofloxacin) resistant *S.* Typhi are highly prevalent now rely on third generation cephalosporins (ceftriaxone, Cefixime, cefotaxime, and cefoperazone) (Acharya *et al.* 1995; Islam *et al.* 1993) and azithromycin to treat typhoid fever (Pokharel *et al.* 2017). These drugs currently remain effective in most countries. However, reports of *S.* Typhi with resistance to third generation cephalosporins have

been emerging in Asia (India (Gokul, Menezes and Harish 2010), Bangladesh (Ahmed *et al.* 2012), Pakistan (Munir *et al.* 2016), Philippines (Al Naiemi *et al.* 2008)), sub-Saharan Africa (DRC (Phoba *et al.* 2017), Nigeria (Akinyemi *et al.* 2017; Akinyemi *et al.* 2015)), and others (Iraqi returner from Iraq Kurdistan region to Germany (Pfeifer, Matten and Rabsch 2009) and traveller from Guatemala to Spain (González-López *et al.* 2014).

Numerous studies have described *S.* Typhi isolates carrying extended-spectrum beta-lactamase (ESBL) enzymes, such as CTX-M types, SHV-12, and AmpC of ACC-1 type, causing resistance to newer beta-lactam antimicrobials including cephalosporins (Aga Khan University Team Investigates Outbreak Of Antibiotic Resistant Typhoid Fever – Take on Typhoid). Azithromycin remains highly effective in clearing *S.* Typhi, possibly due to its ability to concentrate inside cells (Parry *et al.* 2015; Pascual *et al.* 1995), but treatment failure with azithromycin are beginning to be reported in India (Manesh *et al.* 2017).

In 2016 and 2018, outbreaks of extensively drug-resistant (XDR) typhoid fever occurred in Pakistan (Hyderabad and Karachi, respectively) (Qamar *et al.* 2018; Yousafzai *et al.* 2019; Klemm *et al.* 2018) and travellers from the United Kingdom (Klemm *et al.* 2018) and the United States (Chatham-Stephens *et al.* 2019) returning from Pakistan. (XDR *S.* Typhi is defined as resistance to almost all classes of antimicrobials: first-line drugs (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole), fluoroquinolones (ciprofloxacin), and third-generation cephalosporins (typically ceftriaxone)).

1.4.2 Antimicrobial resistance in invasive nontyphoidal *Salmonella*

Historically, co-trimoxazole, ampicillin and chloramphenicol were the first-line drug of choices for typhoid fever and iNTS infections in Africa (Kariuki *et al.* 2015a). However, AMR and MDR iNTS (predominantly *S.* Typhimurium and *S.* Enteritidis) have emerged and spread across sub-Saharan African countries since the late 1980 and early 1990s (Okoro *et al.* 2012; Gordon *et al.* 2008). Various countries in sub-Saharan Africa have reported high prevalence of MDR iNTS infections, including Malawi (Gordon *et al.* 2008; Molyneux *et al.* 2009; Musicha *et al.* 2017), Kenya (Kariuki and Onsare 2015; Oneko *et al.* 2015; Akullian *et al.* 2018), Ghana (Nielsen *et al.* 2012), Gambia (Enwere *et al.* 2006), Democratic Republic of Congo (Kalonji *et al.* 2015), Mozambique (Mandomando *et al.* 2009a; Sigaúque *et al.* 2009), Tanzania (Blomberg *et al.* 2007), Burkina Faso, Guinea-Bissau (Marks *et al.* 2017) and Nigeria (Obaro *et al.* 2015). The wide distribution of MDR iNTS poses a significant challenge for the treatment and management of iNTS disease in Africa as MDR may also be associated with an increased case fatality rate and prolonged transmission (Kariuki *et al.* 2015a). As a result, alternative drugs, such as ciprofloxacin and ceftriaxone, have become increasingly used for the management of sepsis. However, these alternative drugs are more expensive and less widely available in many resource-limited settings in Africa (Molyneux *et al.* 2009; Kariuki *et al.* 2015a). Alarmingly, the effectiveness of these drugs have been diminished due to the emergence of ceftriaxone resistant MDR *S.* Typhimurium ST313 carrying $bla_{\text{CTXM-15}}$ and various MDR associated resistant genes in Kenya (Kariuki *et al.* 2015a) and Malawi (Feasey *et al.* 2014).

In Kenya, patients infected with the ceftriaxone resistant *S.* Typhimurium ST313 were initially treated with ceftriaxone and failed to respond (Kariuki *et al.* 2015a). Notably,

S. Typhimurium ST313 isolates carry the $bla_{\text{CTXM-15}}$ gene cassette on a large conjugative IncHI2 MDR plasmid, which can be transferred to other iNTS serovars and other members of Gram-negative pathogens. Currently, fluoroquinolone resistance in iNTS serovars remains uncommon; however, iNTS with reduced susceptibility to ciprofloxacin have been reported in Burkina Faso (Marks *et al.* 2017) and Ghana (Nielsen *et al.* 2012; Marks *et al.* 2017), Nigeria (Akinyemi, Bamiro and Coker 2007), Senegal (Harrois *et al.* 2014), Mozambique (Mandomando *et al.* 2009a) and Congo (Lunguya *et al.* 2013). It is likely that the widespread use of ceftriazone and ciprofloxacin for the treatment of febrile illnesses in Africa will eventually lead to a rapid increase and spread of MDR pathogens in this continent, which may amplify the burden of the disease. Antimicrobial stewardship and the development of polyvalent vaccine against iNTS serovars are urgently needed for the management and prevention of iNTS infections in Africa.

1.5 The genomic epidemiology of invasive *Salmonella*

The prevention and control of infectious diseases such as invasive salmonellosis are critical for public and global health. Conventional epidemiology and microbiology have played an important role in understanding the incidences of the disease burden, host risk factors, and rise of AMR pathogens. However, advancement in DNA sequencing technology now permits high-throughput whole genome sequencing (WGS) of pathogens (generation of high resolution bacterial nucleic acid sequence data, allowing the identification of single base changes within entire genomes), and ushered in a new era of genomic epidemiology (Tang *et al.* 2017). Now, in-depth investigations of pathogen populations, evolution, transmission dynamics, genetic determinants of AMR, and temporal and spatial dynamics of AMR pathogens can be investigated at a

population level (Baker *et al.* 2018). Next generation sequencing serves as a powerful tool in which to study the emergence and spread of epidemic or/and AMR clones of pathogens, which is critical for better control and treatment of infectious diseases (Parkhill and Wren 2011). New genomic insights into AMR typhoidal and nontyphoidal *Salmonella* in sub-Saharan Africa are being generated, filling a knowledge gap that conventional blood culture and serologic approaches cannot.

1.5.1 The genomic epidemiology of typhoid fever

The genomic era of typhoid started with the first complete genome sequence of a MDR *S.* Typhi (CT18) in 2001 (Parkhill *et al.* 2001). In the last two decades, genomic epidemiological investigations of typhoid fever in Asia and Africa have provided unprecedented insights into the emergence and global dissemination of a particular clone of *S.* Typhi haplotype 58 (H58), which are largely associated with an MDR phenotype. A recent publication, isolates collected from 63 countries between 1992 and 2013 suggested *S.* Typhi H58 (genotype 4.3.1) probably emerged in South Asia late 1980s and subsequently spread to Southeast Asia, Africa and Fiji (Wong *et al.* 2015). The population structure of H58 *S.* Typhi comprises two lineages: lineage I circulating in Southeast Asia (Vietnam, Cambodia, and Laos) with evidence of transmission to Africa; and lineage II in South Asia (mostly India, Nepal, and Pakistan), which is occasionally transferred into Africa (Wong *et al.* 2015). H58 *S.* Typhi are predominantly associated with a PST6 IncHI1 MDR plasmid.

The global spread of MDR H58 *S.* Typhi has led to the increased use of high dose fluoroquinolones as the empirical choice of drug in countries where H58 are circulating. More recently, H58 MDR *S.* Typhi isolates from Southeast Asia were reported with

gyrA mutations, contributing to reduced susceptibility to fluoroquinolones, although the majority of African MDR H58 isolates did not possess *gyrA* mutations (Wong *et al.* 2015). Genomic analysis further revealed the MDR gene cassette (Tn2670-like) is primarily found on a plasmid, but can also inserted into the chromosome (Wong *et al.* 2015). In Africa, WGS and bacterial genomics have been adopted in a number of epidemiological studies, providing new insights into the transmission of various MDR *S.* Typhi genotypes, such as the circulation and clonal expansions of H58 *S.* Typhi in respective countries and characterisations of antimicrobial resistance genes detected (Malawi (Feasey *et al.* 2015), Kenya (Kariuki *et al.* 2010), Guinea (Baltazar *et al.* 2015), Zambia (Hendriksen *et al.* 2015)).

1.5.2 The genomic epidemiology of iNTS disease

Prior to the WGS, pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST), based on a bacterial genomic fingerprint and profile of housekeeping genes, respectively, have identified *S.* Typhimurium ST313 as the primary cause of iNTS disease in Africa (Kenya and Malawi) (Crump and Heyderman 2015). WGS, which provides greater phylogenetic resolution than MLST, has revealed mechanisms of bacterial adaptation by identifying genetic characterizations of AMR ST313, such as resistance genes and associated plasmids and chromosome (Crump and Heyderman 2015). A recent WGS-based phylogenetic analysis of 129 *S.* Typhimurium isolates from seven African countries (Malawi, Kenya, Mozambique, Uganda, The Democratic Republic of Congo (DRC), Nigeria and Mali) in context of the 179 isolates isolated between 1938 and 2010 from various parts of the world, aimed to determine the population structure of African *S.* Typhimurium (Okoro *et al.* 2012). Two closely related but distinct ST313 phylogenetic lineages of invasive *S.* Typhimurium were

identified. These lineages were estimated to have emerged independently around 1960 (lineage I) and 1977 (lineage II) and were temporally associated with the development of the HIV pandemic in Africa (Okoro *et al.* 2012). The sequence data implied the clonal replacement of lineage I (disappeared between 2003-2005) by lineage II (isolates after 2006 were exclusively in lineage II) and possibly associated with the use of chloramphenicol for the iNTS disease treatment in Africa. Lineage I did not possess the chloramphenicol resistance (*cat*) gene, in contrast to >97% of isolates in lineage II (Okoro *et al.* 2012). Limited data suggests that Malawi served as the hub for the emergence and spread of ST313 lineage I in East and Southern Africa (from Malawi to Kenya, DRC, Uganda, and Mozambique). The DRC, and more recently Malawi, have been associated with the transmission of ST313 lineage II to neighbouring countries in East (from DRC to Uganda, Kenya, and Malawi) and further to West Africa (from Malawi to Mozambique, Nigeria, and Mali) (Okoro *et al.* 2012). A distinct composite Tn*21*-like transposition elements, encoding MDR determinants, were identified on pSLT (virulence-associated plasmid) in both lineages of *S.* Typhimurium (Okoro *et al.* 2012).

S. Enteritidis has been repeatedly responsible for epidemics of poultry-associated self-limiting enterocolitis in developed countries during the 1980s (Rodrigue, Tauxe and Rowe 1990). This serovar is being increasingly identified as a common cause of iNTS in sub-Saharan Africa. The *Salmonella* virulence plasmid pSEV, which carries virulence determinants such as the *spvRABCD* locus, have been identified in *S.* Enteritidis, which increases its ability for intracellular proliferation (Rodríguez *et al.* 2012) in human populations in sub-Saharan Africa (Muvhali *et al.* 2017). This plasmid also harbours numerous resistance genes (*bla*TEM-1, *catA2, strA-strB, sul1, sul2, tet*(A)) and a class-

1 integron, conferring resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, tetracycline, and trimethoprim (Rodríguez *et al.* 2012). MDR *S.* Enteritidis isolates reported from clinical specimens collected in the United Kingdom during 2005-2010 also carried pUO-SeVR1-like plasmids (Rodríguez *et al.* 2012).

A recent WGS analysis of 675 *S.* Enteritidis isolates collected from 45 countries and six continents between 1948 and 2013 (largely invasive and non-invasive human clinical samples, and samples from animal, food or environmental sources), suggested a 'global epidemic clade' and two novel African epidemic clades, each geographically restricted to distinct regions of Africa ('Central/Eastern African clade' and 'West African clade') (Feasey *et al.* 2016). The majority of previous studies regarding *S.* Enteritidis suggested isolates belonged the global epidemic clade and were related with enterocolitis in developed countries. Feasey *et al.* recognized that African clades were associated with AMR/MDR and invasive disease: 82% of *S.* Enteritidis in the Central/Eastern African clade were MDR; and 94% of isolates from the West African clade were resistant to one antimicrobial class (Feasey *et al.* 2016).

A temporal reconstruction estimated the most recent common ancestor (MRCA) of the global epidemic, Central/Eastern African, and West African clades was around 1918, 1945, and 1933, respectively (Feasey *et al.* 2016). Overall, the *S.* Enteritidis virulence plasmid (pSENV) was found in most isolates in Africa, indicative of its stable maintenance in each lineage. This plasmid is not self-transmissible as it contains an incomplete set of *tra* genes that is responsible for conjugative system, suggesting that it has been independently acquired on multiple occasions in Africa. Notably, the virulence plasmids from the African clades were much larger (~90kb) than the generic *Salmonella*

virulence plasmids (58kb), and plasmids from West African isolates carried chloramphenicol resistant gene (*cat*A1) while Central/Eastern African isolates carried *cat*A2 and tetracycline resistance gene *tet*(A) (Feasey *et al.* 2016).

1.6 Aims of thesis

Invasive salmonellosis remains a significant public health threat in resource-limited settings in Africa. The situation is currently exacerbated by the emergence and widespread of multidrug resistance rendering inexpensive and widely available antimicrobials ineffective. The epidemiology of invasive salmonellosis in Africa is highly complex with multiple co-circulating *Salmonella* serotypes exhibiting different propensity to develop multidrug resistance and might have dissimilar modes of transmission. In addition, risk factors and predominant mode of the disease transmission are not totally understood. To better tackle the disease, several epidemiological investigations have incorporated genomics in the last decade as an essential component to provide in-depth understanding of the bacterial transmission dynamics and antimicrobial resistance determinants as well as to trace outbreaks of invasive salmonellosis in African countries. Such approaches are essential to gain further insights into the complex disease epidemiology; however, their utility has been hindered by a lack of sequencing facility and a comprehensive standardised surveillance across multiple African regions. Consequently, there is an urgent need of routine surveillance of multidrug resistant invasive salmonellosis in Africa; particularly, in the light of genomics to inform appropriate and timely public health control measures and to improve clinical practice guidelines.

In this thesis, I aimed to investigate the phylogenetics and genomic epidemiology of

enteric fever caused by typhoidal and invasive nontyphoidal *Salmonella* and NTS isolated from a standardised multi-country surveillance in sub-Saharan Africa. My study objectives included a detailed characterization of population structure, transmission dynamics and antimicrobial resistance of predominant invasive *Salmonella* serotypes across African countries. I also aimed to estimate the population-based incidence estimates of MDR invasive salmonellosis across different settings to identify high-risk areas and populations for implementing appropriate interventions. This work also covered an investigation of the association between malaria infection and invasive nontyphoidal *Salmonella* disease as well as a study about the prevalence and genetic characteristics of nontyphoidal *Salmonella* carriage in the general human populations. The specific objectives of this study are as follows:

In Chapter 3, I aimed to further explore the existing hypothesis on the positive correlation between iNTS disease and malaria in sub-Saharan Africa. For this piece of work, clinical and laboratory data were collected through fever surveillance in ten sub-Saharan African countries between 2010 and 2014. I analysed data regarding the age-stratified frequencies of organisms isolated from blood culture and how they related to malaria diagnostic screening. I aimed to correlate iNTS disease and malaria at individual (human host) and geographical (malaria endemic settings compared with areas with lower malaria burden) levels, using univariate and multivariable analyses. The clinical characteristics of febrile patients with iNTS disease were also studied in comparison to that of typhoid fever and other bacteremia.

In Chapter 4, I aimed to assess the phylogeography and incidence of MDR typhoid fever in sub-Saharan Africa. To define the population structure and dynamics of

AMR/MDR *S.* Typhi circulating in the continent, isolated organisms were WGS and subjected to bioinformatics analyses. *S.* Typhi isolates yielded in my study were further analysed in context of the phylogeography of an existing global collection of *S.* Typhi. I further investigated the geographical distribution of various *S.* Typhi genotypes (and MDR organisms) across the African continent. Lastly, I aimed to calculate the incidence of MDR typhoid fever in the respective sub-Saharan African countries.

In Chapter 5, I aimed to describe the phylogenetic structure and incidence estimations of MDR iNTS disease in sub-Saharan Africa. I focussed on the geographical distribution of iNTS genotypes and serovars in sub-Saharan Africa, and characterised their AMR/MDR patterns including resistance genes and plasmids. I performed further phylogeographical analysis of *S.* Typhimurium sequence type 313 (ST313) lineage II and *S.* Enteritidis ST11 with the global collection of respective strains available and published.

In Chapter 6, I aimed to assess the serovar distribution and AMR composition of *Salmonella* isolates from stool in the general human population in two African sites (Senegal and Guinea-Bissau). Stool samples were collected from random households in two study sites and cultured. To determine the phylogenetic relationship between NTS isolates from stool versus blood, isolates were subjected to WGS and phylogenetic analysis was performed. AMR genes and plasmid profiles were also investigated in the NTS isolates from stool and compared to the iNTS isolates described in Chapter 5.

Chapter 2 Methodology

2.1 Typhoid fever surveillance in Africa Study

2.1.1 Study design and inclusion criteria

Between 2010 and 2014, standardized healthcare facility-based surveillance of invasive *Salmonella* infections in sub-Saharan African populations was conducted in thirteen sites in ten countries (Typhoid Fever Surveillance in Africa Program, TSAP) (Von Kalckreuth *et al.* 2016). Febrile patients from all age groups (except in Ghana, where only children aged <15 years were enrolled) with a tympanic or axillary temperature of ≥38.0℃ or ≥37.5℃, respectively, living in a defined study catchment areas were eligible for recruitment. For inpatients, reported fever within the period of 72 hours prior to admission was added to the inclusion criteria. Eligible patients meeting the study inclusion criteria were sought and were required to provide written informed consent. For children, the written informed consent was provided by a parent or guardian. Study staff collected the inclusion criteria and basic demographic data of those consented eligible patients such as age, sex, and location of residency with coded study IDs. Clinical assessment of patients were performed by study physicians, including history and current of illness, physical examination, and clinical appraisal. Eligible patients were treated per the respective national guidelines. Blood samples (5-10 mL for adults; 1-3 mL for children) were collected for laboratory diagnostics of these febrile cases. Treating physicians and subsequently patients were informed of the test result: positive blood cultures were communicated immediately for appropriate discussions on treatment options and implications; negative blood cultures were reported after a minimum five-day incubation period (Von Kalckreuth *et al.* 2016).

2.1.2 Study area and populations

Thirteen sites in ten countries in sub-Saharan Africa were targeted (Figure 2.1): Nioko and Polesgo, Burkina Faso; Butajira, Ethiopia; Asante Akim North District, Ghana; Bissau, Guinea-Bissau; the Kibera informal settlement in Nairobi, Kenya; Imerintsiatosika and Isotry, Madagascar; Pikine, Senegal; Pietermaritzburg, South Africa; East Wad Medani, Sudan; and Moshi Urban and Moshi Rural, Tanzania. Based on a set of site selection criteria, potential study areas were assessed, including study population demographics, logistical feasibility and suitability, existing capacity of laboratory infrastructures and data management, prior experience and potential of local collaborators, and local and national government support for the study project (Von Kalckreuth *et al.* 2016). International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH) were in place in study sites in Guinea-Bissau, Burkina Faso, and Ethiopia, supported by comprehensive Health and Demographic Surveillance Systems (HDSSs) that generated a well-characterized population data of the study area. In Kibera-Kenya, a HDSS was implemented by the KEMRI-Centers for Disease Control and Prevention Kenya Collaboration, whereby an active mobilisation was performed during household visits every two weeks, encouraging febrile patients to visit the study sentinel healthcare facility (Von Kalckreuth *et al.* 2016). Study areas in South Africa, Ghana, Tanzania, and Kenya were well-structured with existing surveillance infrastructure. Study areas included urban, urban slum, and rural settings with varying population sizes (Figure 2.2).

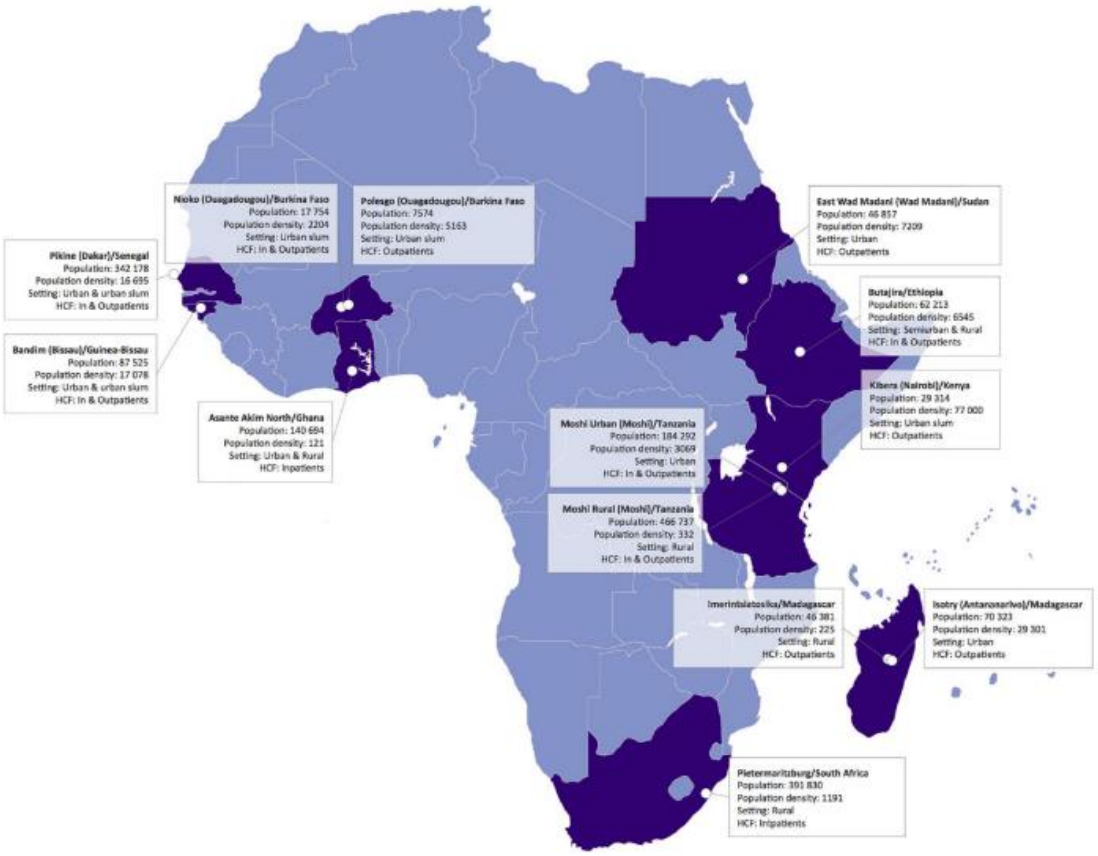


Figure 2.1 The locations of the TSAP sites

Reproduced from Von Kalckreuth *et al*. (2016). Original legend: "Abbreviation: HCF, healthcare facility. Population density, /km^2"

Site profiles are described in boxes corresponding to each locations on the map. **Pikine (Dakar)/Senegal**: Population (342,178), Population density (16,695), Setting (Urban & urban slum), HCF (In & Outpatients). **Bandim (Bissau)/Guinea-Bissau**: Population (87,525), Population density (17,078), Setting (Urban & urban slum), HCF (In & Outpatients). **Nioko (Ouagadougou)/Burkina Faso**: Population (17,754), Population density (2,204), Setting (Urban slum), HCF (In & Outpatients). **Polesgo (Ouagadougou)/Burkina Faso**: Population (7,574), Population density (5,163), Setting (Urban slum), HCF (Outpatients). **Asante Akim North/Ghana**: Population (140,694), Population density (121), Setting (Urban & Rural), HCF (Inpatients). **East Wad Madani (Wad Madani)/Sudan**: Population (46,857), Population density (7,209), Setting (Urban), HCF (Outpatients). **Butajira/Ethiopia**: Population (62,213), Population density (6,545), Setting (Semi-urban & Rural), HCF (In & Outpatients). **Kibera (Nairobi)/Kenya**: Population (29,314), Population density (77,000), Setting (Urban slum), HCF (Outpatients). **Moshi Urban (Moshi)/Tanzania**: Population (184,292), Population density (3,069), Setting (Urban), HCF (In & Outpatients). **Moshi Rural (Moshi)/Tanzania**: Population (466,737), Population density (332), Setting (Rural), HCF (In & Outpatients). **Imerintsiatosika/Madagascar**: Population (46,381), Population density (225), Setting (Rural), HCF (Outpatients). **Isotry/Madagascar**: Population (70,323), Population density (29,301), Setting (Urban), HCF (Outpatients). **Pietermaritzburg/South Africa**: Population (391,830), Population density (1,191), Setting (Rural), HCF (Inpatients).

Country and Survey Site	Collaborating Institution	Setting	Catchment Population Size, No. and Year	Published Data on TF in TSAP Countries	Further Characteristics of TSAP Survey Sites			
					% of Country Population Using Improved [25]:			
					Drinking Water Sources	Sanitation	DSS Site [26]	GNI Per Capita, US $ [27]
South Africa, Pietermaritzburg	NICD	Urban	361 582 (2011)	[28–31]	Total: 91 Urban: 99 Rural: 79	Total: 79 Urban: 86 Rural: 67	No	10 790
Kenya, Kibera	KEMRI–CDC Kenya Collaboration	Urban slum	26 098	[19, 32,33]	Total: 59 Urban: 82 Rural: 52	Total: 32 Urban: 32 Rural: 32	Active surveillance	1720
Tanzania, Moshi	Kilimanjaro Christian Medical Centre/DUKE Collaboration	Rural and urban	545 168 (2002)	[29, 34–36]	Total: 53 Urban: 79 Rural: 44	Total: 10 Urban: 20 Rural: 7	No	1510
Ghana, Asante Akim North Municipal	Kumasi Centre for Collaborative Research in Tropical Medicine	Rural	80 074	[18, 37]	Total: 86 Urban: 91 Rural: 80	Total: 14 Urban: 19 Rural: 8	No	1820
Ethiopia, Butajira	Armauer Hansen Research Institute	Rural and urban	61 965 (2012)	[38]	Total: 44 Urban: 97 Rural: 34	Total: 21 Urban: 29 Rural: 19	Yes	1110
Madagascar, (1) Isotry and (2) Imerintsiatosika	University of Antananarivo	(1) Urban slum (2) Rural	(1) 70 323 (1993) (2) 49 038 (2010)	[39, 40]	Total: 46 Urban: 74 Rural: 34	Total: 15 Urban: 21 Rural: 12	No	950
Senegal, Pikine (Dakar)	Institute Pasteur Senegal	Urban slum	342 178 (2012)	[41, 42]	Total: 72 Urban: 93 Rural: 56	Total: 52 Urban: 70 Rural: 39	No	1960
Burkina Faso, (1) Kossodo and (2) Polesgo	University of Ouagadougou	Urban	(1) 13 846 (2012) (2) 5738 (2012)	[43]	Total: 79 Urban: 95 Rural: 73	Total: 17 Urban: 50 Rural: 6	Yes	1310
Sudan, WadMedani	University of Gezira	Urban	47 935 (2013)	[44]	Total: 58 Urban: 67 Rural: 52	Total: 26 Urban: 44 Rural: 14	No	2020
Guinea-Bissau, Bandim (Bissau)	Bandim Health Project	Urban	100 153 (2012)	No published data	Total: 64 Urban: 91 Rural: 53	Total: 20 Urban: 44 Rural: 9	Yes	1250

Abbreviations: CDC, Centers for Disease Control and Prevention; DSS, Demographic Surveillance System; DUKE, Duke University Medical Center; GNI, Gross National Income; KEMRI, Kenya Medical Research Institute; NICD, National Institute for Communicable Diseases; TF, typhoid fever; TSAP, Typhoid Fever Surveillance in Africa Program.

Figure 2.2 The selected countries and survey sites of the TSAP

Reproduced from Von Kalckreuth *et al.* (2016)**.**

2.2 Randomized stool culture survey of the general population in Senegal and Guinea-Bissau for identifying *Salmonella* excreters

The study (Im *et al.* 2016) was designed as a household-level randomized stool culture survey of the general population in Dakar, Senegal (between January 2013 and June 2014) and Bissau, Guinea-Bissau (June 2012-September 2013). A simple random sample of households from each site was selected, and all individuals living in the dwellings were recruited. Any prior infection or current symptoms at time of enrollment were not exclusion criteria. As such, health status was not used to determine eligibility for participation in the study. Informed consent was obtained from participants, and households were visited the day following recruitment for stool collection. Fresh stool samples were collected in containers and transported at ambient temperature to the site laboratory within six hours of collection for culture (Im *et al.* 2016).

2.3 Sample collection and laboratory investigations

2.3.1 Bacterial identification, antimicrobial susceptibility, and malaria testing

Through the TSAP study, blood specimens were obtained from febrile patients; one aerobic blood culture bottle per patient. Automatic incubating was performed (BACTEC Peds Plus Medium/BACTECT Plus Aerobic-F, BACTEC, Becton-Dickinson, New Jersey; or BacT/ALERT PF Paediatric FAN/BacT/ALERT FA FAN Aerobic, bioMerieux, Marcy l'Etoile, France) except for the study site in Sudan whereby manual blood culture techniques were used (Von Kalckreuth *et al.* 2016). Blood culture process included Gram staining, sub-culturing on blood agar, chocolate agar and MacConkey agar (all Oxoid, Basingstoke, United Kingdom), biochemical reactions for pathogen identification and sero-grouping (Von Kalckreuth *et al.* 2016)**.** Blood cultures with bacterial growth were sub-cultured, and biochemical tests were conducted (API 20E,

bioMerieux) to confirm suspected *Salmonella* isolates.

Antimicrobial susceptibility testing was performed using agar diffusion tests according to the Clinical Laboratory and Standards Institute (CLSI) guidelines. Contaminants were defined as those bacteria commonly belonging to the skin flora including coagulase-negative staphylococci, *Corynebacterium* species, and *Bacillus* species. However, the test results were with patient clinical data to determine atypical or opportunistic infections for each case (Von Kalckreuth *et al.* 2016). Malaria diagnostics were performed via a combination of thick and thin blood smears and rapid malaria test (SD Bioline Malaria Ag P.f./P.v., SD Standard Diagnostics, Suwon, Republic of Korea), this was variable between sites (Park *et al.* 2016). All bacterial isolates were stored (Microbank PL170, Pro-Lab Diagnostics, Round Rock, Texas) at the study sites at -70^{o}C to preserve them for shipment to the reference laboratories for further characterization and reconfirmation (Von Kalckreuth *et al.* 2016)**.**

From the stool culture survey study, stool specimens collected were sent to the laboratory, where stool was suspended in Selenite broth for enrichment and incubated for 24 hours at 36℃ (Im *et al.* 2016). Samples were cultured on xylose lysine deoxycholate agar for selective growth of *Salmonella* and *Shigella* species. Isolates were identified by biochemical reactions and further confirmed by polymerase chain reaction (PCR). Antimicrobial susceptibility testing was also performed by the agar diffusion method (Kirby-Bauer) and assessed by CLSI M100-S23 criteria. A multiplex PCR (Qiagen, Hilden, Germany) was also conducted using targeted selected primers for typing and identification of *Salmonella* serovars (Im *et al.* 2016).

2.3.2 Data sources and bacterial isolates in Chapter 3

Between 2010 and 2014 the TSAP study recruited 13,558 patients meeting the study inclusion, of which 127 patients were excluded due to incomplete data. This resulted in 13,431 patients, with 135 *S.* Typhi isolated from patients in the defined study catchment areas in 9 countries. The laboratory (blood culture confirmed bacterial pathogens, antimicrobial susceptibility, and malaria test results) and clinical data collected were used for the epidemiological analysis presented in Chapter 3.

2.3.3 Data sources and bacterial isolates in Chapter 4

In addition to the 135 *S.* Typhi isolates from the TSAP study as described in chapter 3, *S.* Typhi collected from other studies in Africa, including Uganda (2015; n=30), The Gambia (2008-2014; n=11) and Ghana (2010; n=38) were added. Additional isolates from Ghana (n=33) were from the TSAP study, which had been removed from the analyses in Chapter 3 (these *S.* Typhi patients resided outside of the strictly defined study catchment area) but were included for the bacterial genomic analyses. After whole genome sequencing and data quality screening a total of 249 *S.* Typhi isolates were analysed in Chapter 4. For further analyses on my African *S.* Typhi isolates in a global context, 2,057 *S.* Typhi in a genomic dataset were also included (Wong *et al.* 2015). A detailed summary about these isolates and their country of origin including all the metadata is provided in the appendix.

2.3.4 Data sources and bacterial isolates in Chapter 5

The total of 166 iNTS isolates was used in this chapter, which comprised 94 iNTS isolates from the TSAP study, an additional 23 iNTS isolates detected outside the predefined study catchment area, and 49 iNTS isolates from other studies conducted in

Agogo, Ghana in 2007-2009. For further analyses on the *S.* Typhimurium and *S.* Enteritidis isolates in context of the global phylogeny of respective organisms, existing datasets were incorporated: 102 iNTS serovar Typhimurium ST313 Lineage II isolates from seven countries (Malawi, Kenya, Mozambique, Uganda, DRC, Nigeria, and Mali (Okoro *et al.* 2012), Nigeria and DRC (Leekitcharoenphon *et al.* 2013), Malawi (Feasey *et al.* 2014), Kenya (Kariuki *et al.* 2015a), Malawi (Msefula *et al.* 2012), and 594 iNTS serovar Enteritidis ST11 isolates (selected from Feasey *et al.* 2016). A summary of these isolates and their country of origin including metadata is provided in the appendix.

2.3.5 Data sources and bacterial isolates in Chapter 6

A total 40 of NTS isolates, with associated metadata was generated from the randomized stool culture survey of the general human population in Senegal (January 2013-June 2014) and Guinea-Bissau (June 2012-September 2013) (Im *et al.* 2016). After whole genome sequencing of these NTS isolates, a total 37 NTS organisms were used for analysis in Chapter 6. Details regarding these isolates and their metadata are presented in the appendix.

2.4 Whole genome sequencing

Genomic DNA was extracted from all *Salmonella* isolates using the Wizard Genomic DNA Extraction Kit (Promega, Wisconsin, USA). Two μg of genomic DNA from each organism was subjected to indexed-tagged pair-end sequencing on an Illumina Hiseq 2000 platform (Illumina, CA, USA) to generate 100 bp paired-end reads. Raw sequence data are available in the European Nucleotide Archive (Project number: ERP009684, ERP010763, ERP013866).

2.5 Single Nucleotide Polymorphism (SNP) calling and analyses

2.5.1 SNP analyses of *S.* Typhi in Chapter 4

To identify single nucleotide polymorphisms (SNPs), raw Illumina reads were mapped to the reference sequence of *S.* Typhi CT18 (accession: AL513382) including plasmids pHCM1 (accession: AL513383) and pHCM2 (accession: AL513384), using SMALT version 0.7.4 (Page *et al.* 2016a). Candidate SNPs were called against the reference sequence using SAMtools (Li *et al.* 2009) and filtered with a minimal phred quality of 30 and minimum consensus base agreement of 75%. The allele at each locus in each isolate was determined by reference to the consensus base in that genome using SAMtools *mpileup* and removing low confidence alleles with consensus base quality ≤20, read depth ≤5 or a heterozygous base call. SNPs in phage regions, repetitive sequences, or recombinant regions identified previously were excluded (Wong *et al.* 2015; Holt *et al.* 2008). I further identified an additional recombinant region from the whole genome alignment produced by SNP-calling isolates using Gubbins (Croucher *et al.* 2015) and SNPs detected within this region (~20kb from nucleotide 1,439,032-1,459,472) were removed, resulting in a final set of 4,444 chromosomal SNPs. The SNP data were used to assign all isolates to previously defined subclades in the *S.* Typhi genotyping framework, which included four primary clusters, 16 clades and 49 subclades from more than 1,800 global collection of *S.* Typhi isolates (Wong *et al.* 2016a). *S.* Typhi haplotype 58 (H58) belonged to subclade 4.3.1 according to this genotype nomenclature.

2.5.2 SNP analyses for iNTS isolates in Chapter 5

Raw Illumina reads were used to create multiple assemblies using Velvet v1.2 (Zerbino and Birney 2008) with parameters optimized using VelvetOptimiser v2.2.5 (Gladman

and Seemann. https://github.com/Victorian-Bioinformatics-Consortium/VelvetOptimiser.git; Page *et al.* 2016) and automated annotation was performed using PROKKA v1.5 (Seemann 2014). Roary (Page *et al.* 2015) was used to define the pan genome of 166 iNTS isolates with blastp percentage identity of 99% and a core definition of 99%. 3,450 core genes were identified (genes that present in ≥99% strains) and 86,765 SNP sites were extracted from the core gene alignment using SNP-sites (Page *et al.* 2016b).

For *S.* Typhimurium ST313, raw Illumina reads of 99 isolates from my studies and additional 102 isolates *S.* Typhimurium ST313 lineage II from previous studies (Leekitcharoenphon *et al.* 2013; Kariuki *et al.* 2015a; Okoro *et al.* 2012); Msefula *et al.* 2012; Feasey *et al.* 2014) were mapped to the reference sequence of *S.* Typhimurium strain SL1344 (accession: FQ312003.1), using SMALT version 0.7.4 (http://www.sanger.ac.uk/resources/software/smalt/). Candidate SNPs were called against the reference sequence using SAMtools (Li *et al.* 2009) and filtered with a minimum mapping quality of 30 and minimum consensus base agreement of 75%. The allele at each locus in each isolate was determined by reference to the consensus base in that genome using SAMtools *mpileup* and removing low confidence alleles with consensus base quality ≤20, read depth ≤5 or a heterozygous base call. Repeat finding program in NUCmer v3.1 (Kurtz *et al.* 2004) was used to identify exact repetitive regions of ≥ 20 bp in length in the reference genome and SNPs called in these regions were excluded. SNPs called in phage sequences and recombinant regions identified using Gubbins (Croucher *et al.* 2015) were further removed, resulting in a final set of 1,960 chromosomal SNPs. The identification of SNPs for *S.* Enteritidis ST11 was

performed following the same procedure as *S.* Typhimurium ST313. Briefly, the raw Illumina reads of 28 *S.* Enteritidis ST11 isolates from my studies and additional 594 isolates from a global collection (Feasey *et al.* 2016) were mapped to the reference sequence of *S.* Enteritidis strain P125109 (accession: NC_011294.1), using SMALT followed by SNP calling and filtering as above resulting in a final set of 25121 SNPs.

2.5.3 SNP analyses of *S.* Enteritidis ST11 isolate from stool in Chapter 6

The genomic data of the *S.* Enteritidis ST11 isolate carrying spv virulence plasmid from the human faecal sample was combined with genomic data of 28 *S.* Enteritidis ST11 from my study and the global collection of 594 genomes. Subsequently SNP calling process was performed as described above generating a final set of 25,189 SNPs.

2.6 Phylogenetic analyses

2.6.1 Phylogenetic analysis for *S.* Typhi in Chapter 4

2.6.1.1 Maximum likelihood phylogenetic tree

A maximum likelihood (ML) phylogenetic tree was constructed from the 4,444 SNP alignment using RAxML version 8.2.8 with a generalized time-reversible model and a Gamma distribution to model the site-specific rate variation (GTR+Γ_4 model) (Stamatakis 2014). Branch support for this tree was assessed through a bootstrap analysis with 1,000 pseudo-replicates. To investigate the molecular epidemiology of my African isolates in regional and international context, a secondary ML tree was inferred from a separate alignment of 26,479 SNPs identified across a total of 2,306 *S.* Typhi isolates (249 from this study, 1,830 from the global collection (Wong *et al.* 2015), 128 from Nigeria (Wong *et al.* 2016b), and 99 travel-associated *S.* Typhi organisms isolated in the United Kingdom (Wong *et al.* 2016a) using RAxML with GTRGAMMA

substitution model and *S.* Paratyphi A sequence data to outgroup root the tree. Branch support for this phylogeny was assessed through a 100 bootstrap pseudo-analysis. Annotation of this global tree was visualized using ITOL (Letunic and Bork 2007). An interactive version of the global phylogeny, with organisms labeled by genotype, country of origin, year of isolation and antimicrobial susceptibility was generated in Microreact (Argimón *et al.* 2016).

2.6.1.2 Evolutionary timescales and phylogeographic patterns

For genotype 3.1.1 strains, a Bayesian phylogenetic analyses was conducted in BEAST2 v2.4.7 (Bouckaert *et al.* 2014). The GTR+Γ_4 substitution model, an uncorrelated lognormal relaxed-clock model, and the exponential-growth coalescent tree prior were used. Three independent analyses were performed with 5×10^8 steps, recording samples every 5×10^4 steps. I assessed sufficient sampling by combining the three independent runs and verifying that the effective sample size of all parameters was at least 500. To calibrate the molecular clock, I used the sampling year of all sequences. This analysis also included an outgroup sequence (CT18) to ensure a biologically meaningful root location. My selected molecular clock model and tree prior have been shown to perform well even when the data display low rate variation and constant population size dynamics (Duchêne *et al.* 2016b). This model combination also allowed for informal model testing via the coefficient of rate variation and the population growth rate parameters (Duchêne *et al.* 2016a; Ho, Duchêne and Duchêne 2015). To determine phylogeographic patterns, I considered the country of sampling as a discrete trait in my analysis in BEAST2 (Lemey *et al.* 2009). A potential shortcoming of this analysis was that it included a large number of parameters (transition rates between all locations), therefore the output of these analysis may be impacted by the prior

distribution. I verified that the prior distribution differed from the posterior by comparing the distributions of all transition rates.

An important consideration when using sampling times as calibrations is that the sampling timespan should capture sufficient genetic variation to allow reliable inferences of evolutionary rates and timescales, such that the data have strong temporal structure. I verified the temporal structure in the data by using a root-to-tip regression and a date-randomisation test (Rieux and Balloux 2016). I conducted a root-to-tip regression for the outgroup-rooted ML tree using TempEst (Rambaut *et al.* 2016). For the date-randomisation test we repeated the analysis 20 times while randomising the sampling times. My expectation was that the randomisations should produce evolutionary rate estimates that were lower and that did not overlap with those obtained with the correct sampling times (Duchêne *et al.* 2015). Finally, I compared my estimate of the time of origin of the 3.1.1 lineage in BEAST with an independent method, LSD v0.3 (To *et al.* 2016).

2.6.2 Phylogenetic analysis for iNTS in Chapter 5

2.6.2.1 Maximum likelihood phylogenetic tree

A maximum likelihood (ML) phylogenetic tree was constructed from the 86,765 SNP alignment of all 166 iNTS isolates using RAxML version 8.2.8 with a generalized time-reversible model and a Gamma distribution to model the site-specific rate variation (GTRGAMMA in RAxML) (Stamatakis 2014). Clade support for this tree was assessed through a bootstrap analysis with 100 pseudo-replicates. To investigate the molecular epidemiology of my *S.* Typhimurium ST313 and *S.* Enteritidis ST11 isolates in regional and international context, ML tree was inferred from an alignment of 1,960 SNPs for

201 *S.* Typhimurium ST313 lineage II isolates (99 from this study and 102 from previous studies (Okoro *et al.* 2012; Leekitcharoenphon *et al.* 2013; Feasey *et al.* 2014; Kariuki *et al.* 2015a; Msefula *et al.* 2012) and an alignment of 25,121 SNPs for 622 *S.* Enteritidis ST11 isolates (28 from this study and 594 from a global collection (Feasey *et al.* 2016)), using RAxML with the same parameters as above. Support for these phylogenetic trees was assessed through a 100 bootstrap pseudo-analysis. Tree annotation was visualized using ITOL (Letunic and Bork 2007).

2.6.3 Phylogenetic analysis for NTS in Chapter 6

2.6.3.1 Maximum likelihood phylogenetic tree

The phylogenetic relationship between the *S.* Enteritidis ST11 isolate from the stool carrying IncF virulence plasmid and 28 *S.* Enteritidis ST11 isolates from bloodstream infections in Chapter 5 as well as the global collection of 594 *S.* Enteritidis ST11 isolates was performed by reconstructing the maximum likelihood tree from their SNP alignment (25,189 SNPs) using RAxML version 8.2.8 with a generalized time-reversible model and a Gamma distribution to model the site-specific rate variation (GTRGAMMA in RAxML) (Stamatakis 2014). Tree annotation was performed using ITOL (Letunic and Bork 2007).

2.6.3.2 Minimum spanning tree

To characterize the genetic relationship between the 37 NTS isolates from stool samples, a minimum spanning tree was reconstructed from their allelic profiles using goeBURST algorithm implemented in PHYLOViZ software (Francisco *et al.* 2012). Two sequence types were grouped into a single clonal complex if they share at least five out of the seven alleles in the MLST scheme.

2.7 Antimicrobial resistant gene and plasmid analyses

2.7.1 Antimicrobial resistance gene and plasmid analyses for *S*. Typhi (Chapter 4)

ARIBA (Antimicrobial Resistance Identifier by Assembly) (Hunt *et al.* 2017) and CARD (https://card.mcmaster.ca/home) were used to investigate AMR gene content. ARIBA reported the AMR genes and the quality of assemblies and variants detected between the sequencing reads and the reference sequences, including mutations in the quinolone resistance-determining region (QRDR) of the *gyrA*, *gyrB*, *parC*, and *parE* genes. For plasmid identification, the sequence reads from each isolate were *de novo* assembled using the short-read assembler Velvet with parameters optimized by Velvet Optimizer (Zerbino and Birney 2008; Page *et al.* 2016). Contigs that were <300 bp long were excluded and the assembled contigs were annotated using Prokka (Page *et al.* 2016; Seemann 2014). Plasmid typing was performed *in silico* using PlasmidFinder (Carattoli *et al.* 2014). The presence of the IncHI1 plasmid was confirmed by BLASTN by searching the assembled sequences in reference to the pHCM1 reference plasmid sequence, and comparative analyses were performed and visualized using ACT (Carver *et al.* 2008). IncHI1 plasmid sequence types were identified using SRST2 software (Inouye *et al.* 2014) with the IncHI1 plasmid MLST scheme (Phan *et al.* 2009). To investigate the isolates with MDR phenotype and without plasmid, raw sequences were subjected to *de novo* genome assembly using SPAdes version 3.11.0 (Bankevich *et al.* 2012), and the resulting assembly graph was visualized in Bandage (Wick *et al.* 2015) to inspect the location of AMR genes in the genome.

2.7.2 Antimicrobial resistance gene and plasmid analyses for iNTS (Chapter 5) and NTS (Chapter 6)

From raw Illumina reads, Short Read Sequence Typer- SRST2 (Inouye *et al.* 2014) was used to identify the acquired AMR genes and their precise alleles using the ARG-Annot database (Gupta *et al.* 2014), as well as the plasmid replicons using the PlasmidFinder database (Carattoli *et al.* 2014). Multilocus sequence typing (MLST) of all iNTS isolates was also determined using SRST2 together with MLST database for *Salmonella enterica* downloaded from pubMLST. *Salmonella* serovars were identified using conventional serology as well as MLST (Achtman *et al.* 2012) and genomics (Zhang *et al.* 2015). To investigate the isolates with resistant genotypes, a *de novo* genome assembly was performed from raw sequences using SPAdes (Bankevich *et al.* 2012) version 3.11.0, followed by Bandage (Wick *et al.* 2015) to inspect the location of AMR genes in the corresponding assembled contigs.

2.8 Statistical analyses

2.8.1 Statistical analysis in Chapter 3

The frequency proportions of bacteremias and *Plasmodium* parasite positivity are presented. After performing a normality test, potential correlations between malaria and bacteremias were identified with the Spearman correlation coefficient (r). To calculated odds ratios (ORs) of iNTS infections per exposure to malaria endemicity (proportion of malaria frequencies at health facilities used as a proxy) I used a generalized estimating equation (GEE) logistic regression. Stratified logistic regression for the univariate and multivariable analyses were performed to identify the individual-level covariates including *Plasmodium spp.* parasite positivity and anaemia, which are considered to be associated with iNTS disease. Data were analysed taking into account age groups, sex,

site-specific characteristics, and clinical data using Microsoft Excel (version 9.0, Microsoft Corporations, Redmond, Washington) and SAS software (version 9.4, SAS Institute, Cary, North Carolina).

2.8.2 Incidence analyses of MDR *S.* Typhi and MDR iNTS in Chapters 4 and 5

Incidence of MDR *S.* Typhi was estimated per 100,000 person-years of observation (PYO) for MDR *S.* Typhi isolates found in Ghana, Kenya and Tanzania and MDR iNTS isolates detected from Burkina Faso, Ghana, Guinea-Bissau, Kenya, and Senegal. Statistical methodology used previously to calculate the incidence of *S.* Typhi and iNTS disease in TSAP countries was used to calculate MDR *S.* Typhi incidence (Marks *et al.* 2017; Von Kalckreuth *et al.* 2016; Panzner *et al.* 2016). Briefly, an age-stratified PYO were estimated using available demographic data in HDSS (Health and Demographic Surveillance System) and non-HDSS sites and health-seeking behaviour of randomly selected individuals, representative of the study population, were factored in (denominator). The recruitment proportion was adjusted to the age-stratified crude MDR *S.* Typhi and MDR iNTS cases (numerator). Adjusted incidence of MDR *S.* Typhi and MDR iNTS per 100,000 PYO was estimated with 95% CIs using these adjustment factors and crude MDR *S.* Typhi and MDR iNTS case numbers. The previously established multi-country database (FoxPro software) for TSAP was used for the countries with MDR *S.* Typhi and MDR iNTS isolates. The incidence of MDR *S.* Typhi in Uganda could not be measured, as data regarding adjustment factors (healthcare seeking behaviour and recruitment proportion) was unavailable at the time of analysis.

Chapter 3 The relationship between invasive nontyphoidal *Salmonella* disease, other bacterial bloodstream infections, and malaria in sub-Saharan Africa

All work described in Chapter 3 was published in the journal of Clinical Infectious Diseases during my DPhil (See Appendix) (Park *et al.* 2016).

3.1 Abstract

The association between *Plasmodium falciparum* and invasive nontyphoidal *Salmonella* (iNTS) disease has been reported in multiple country-specific studies in Africa. Here, I performed a multi-centre surveillance of febrile patients in 13 sites in 10 countries: Burkina Faso, Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, Sudan, and Tanzania. Between 1 March 2010 and 31 January 2014, total 13,431 febrile patients were enrolled for collection of clinical data and blood sample for blood culture and malaria test. A positive correlation between the iNTS disease and frequency proportions of malaria parasitemia was found (p=0.01; r=0.70). The study areas with higher burden of malaria exhibited higher odds of iNTS disease compared to other bacterial infections (odds ratio [OR], 4.89; 95% confidence interval [CI], 1.61-14.90; p=0.005) than areas with lower malaria burden. Malaria parasitemia associated with iNTS disease (OR, 2.44; p=0.031) and Gram-positive bacteremias such as *Staphylococcus aureus*. *S.* Typhimurium and *S.* Enteritidis were the predominant iNTS serovars (53/73; 73%). Both moderate and severe anaemias were associated with iNTS disease: OR, 6.05; p=0.0001 and OR, 14.62; p<0.0001), respectively. These results suggest the necessity of adequate diagnostics and treatments of febrile illnesses, and

prevention of iNTS disease through iNTS vaccines, especially targeting high-risk groups for *Plasmodium* parasitic infection in areas or countries of high malaria endemicity.

3.2 Introduction

NTS infections can result in invasive disease in specific populations in sub-Saharan Africa. iNTS disease is typically characterized by nonspecific and diverse clinical features, making it difficult to differentiate from other febrile illnesses, including typhoid fever (Gordon *et al.* 2010; MacLennan and Levine 2013). Scientifically robust data regarding the incidence of iNTS disease in Africa is lacking, but a systematic review of the global burden of iNTS disease in 2010 estimated 3.4 million cases with a case fatality rate of 20%, Africa having the highest burden of arising iNTS disease (Ao *et al.* 2015; Reddy, Shaw and Crump 2010). Several investigations on the host risk factors of iNTS disease have been performed, which identified recent malaria (Mabey, Brown and Greenwood 1987), human immunodeficiency virus (HIV) (Gordon *et al.* 2002), severe anaemia (Calis, Phiri and van Hensbroek 2008), severe malnutrition (Bachou *et al.* 2006), and sickle cell disease (MacLennan 2012; Morpeth, Ramadhani and Crump 2009) as being associated with iNTS disease. However, further studies are warranted to better understand the natural history of iNTS infections, including the transmission dynamics of iNTS organisms, the clinical features, such as asymptomatic human infections, symptomatic and systemic disease, disease reservoirs, and the immune responses upon infection.

Globally, 198 million cases (584,000 deaths) of malaria were reported in 2013; 90% of the cases originated in sub-Saharan Africa (World Health Organization). The burden of

malaria correlates with the rate of susceptible individuals that are infected and that acquire the disease; infants and young children remain at high risk in highly malaria endemic settings (Griffin, Ferguson and Ghani 2014). Inadequate microbiological laboratory infrastructure in resource limited settings often results in misdiagnosis of bacteremia with malaria (Nankabirwa *et al.* 2009). In high-malaria transmission areas, older children and adults may be infected with *Plasmodium falciparum* with existing partial immunity that may prevent the development of clinical symptoms (Marks *et al.* 2005). Patients with iNTS disease often have nonspecific clinical characteristics (MacLennan and Levine 2013) and may be treated with antimalarials and/or inappropriate antimicrobials. Further, pre-existing antimicrobial regimens are becoming less effective for treating increasingly drug-resistant malaria (Plowe 2009) and antimicrobial resistant iNTS organisms (Oneko *et al.* 2015; Eibach *et al.* 2016; Kariuki *et al.* 2015a). The relationship between iNTS disease and malaria has been investigated (Mabey, Brown and Greenwood 1987; Mtove *et al.* 2011) but generally restricted to a site-/country-specific study. Here, I investigated the epidemiology of iNTS disease and malaria in the context of community-acquired bacteraemia through standardized fever surveillance across ten sub-Saharan African countries.

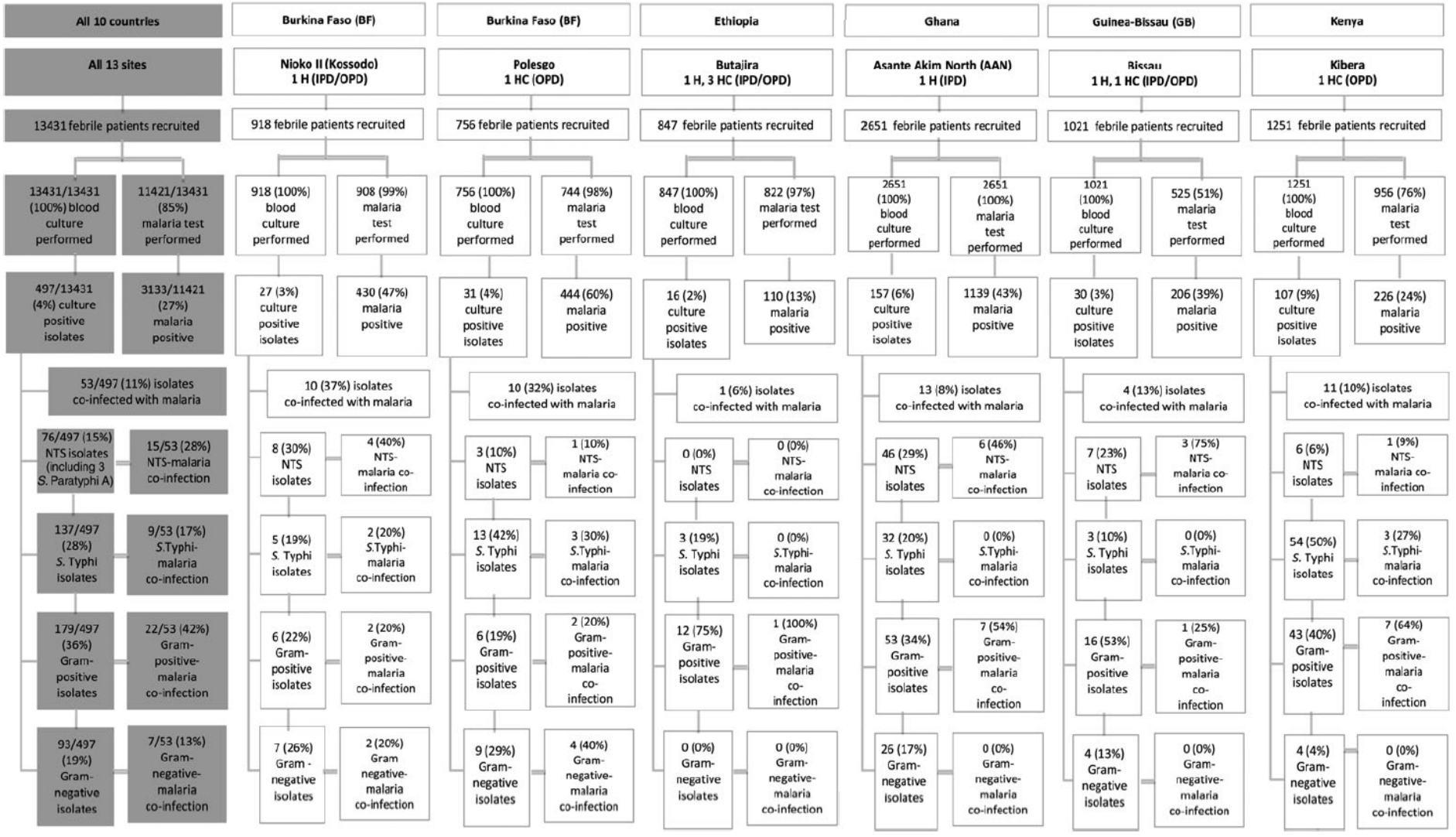
3.2 Results

3.2.1 Organisms isolated from blood culture and malaria testing

From 2010-2014, a total of 13,431 febrile patients were enrolled and had a blood culture performed. Of the 13,431 blood cultures, 497 (4%) were positive for a bacterial pathogen: 73 (15%) iNTS (*S.* Typhimurium [n=38/73; 52%], *S.* Enteritidis [n=15/73; 21%], *S.* Dublin [n=10/73; 14%], and several other undetermined *Salmonella* serovars [n=10/73; 14%]); 3 (1%) *S.* Paratyphi A; 137 (28%) *S.* Typhi (*S.* Typhi); and 272 (55%)

non-*Salmonella* bacteremias (179/272 [66%] Gram-positive and 93/272 [34%] non-*Salmonella* Gram-negative bacteremias). The proportion of iNTS among positive blood cultures was the highest in Nioko, Burkina Faso (8/27; 30%) and Asante Akim North, Ghana (46/157; 29%), although the proportion of Gram-positive bacteremias was equivalently high in the latter (Figure 3.1).

A total of 11,421 of 13,431 (85%) blood samples were screened for malaria, of which 3,133 (27%) were positive by any of the selected malaria tests. The proportion of malaria frequencies presenting at healthcare facilities was the highest in Polesgo, Burkina Faso (444/744; 60%) and Nioko, Burkina Faso (430/908; 47%), followed by Asante Akim North, Ghana (1139/2651; 43%), and East Wad Medani, Sudan (254/632; 40%). Sites in Ethiopia, Madagascar, and Tanzania had the lowest proportion of malaria-positive results. All, with the exception of 20 *Plasmodium malariae* and 2 *Plasmodium ovale* infections in Asante Akim North, Ghana and with 332 missing data on the *Plasmodium* species, were *P. falciparum* monoinfections.


All 10 countries
All 13 sites
13431 febrile patients recruited
13431/13431 (100%) blood culture performed
11421/13431 (85%) malaria test performed
497/13431 (4%) culture positive isolates
3133/11421 (27%) malaria positive
53/497 (11%) isolates co-infected with malaria
76/497 (15%) NTS isolates (including 3 S. Paratyphi A)
15/53 (28%) NTS-malaria co-infection
137/497 (28%) S. Typhi isolates
9/53 (17%) S.Typhi-malaria co-infection
179/497 (36%) Gram-positive isolates
22/53 (42%) Gram-positive-malaria co-infection
93/497 (19%) Gram-negative isolates
7/53 (13%) Gram-negative-malaria co-infection
Burkina Faso (BF)
Nioko II (Kossodo)
1 H (IPD/OPD)
918 febrile patients recruited
918 (100%) blood culture performed
908 (99%) malaria test performed
27 (3%) culture positive isolates
430 (47%) malaria positive
10 (37%) isolates co-infected with malaria
8 (30%) NTS isolates
4 (40%) NTS-malaria co-infection
5 (19%) S. Typhi isolates
2 (20%) S.Typhi-malaria co-infection
6 (22%) Gram-positive isolates
2 (20%) Gram-positive-malaria co-infection
7 (26%) Gram - negative isolates
2 (20%) Gram negative-malaria co-infection
Burkina Faso (BF)
Polesgo
1 HC (OPD)
756 febrile patients recruited
756 (100%) blood culture performed
744 (98%) malaria test performed
31 (4%) culture positive isolates
444 (60%) malaria positive
10 (32%) isolates co-infected with malaria
3 (10%) NTS isolates
1 (10%) NTS-malaria co-infection
13 (42%) S. Typhi isolates
3 (30%) S.Typhi-malaria co-infection
6 (19%) Gram-positive isolates
2 (20%) Gram-positive-malaria co-infection
9 (29%) Gram-negative isolates
4 (40%) Gram-negative-malaria co-infection
Ethiopia
Butajira
1 H, 3 HC (IPD/OPD)
847 febrile patients recruited
847 (100%) blood culture performed
822 (97%) malaria test performed
16 (2%) culture positive isolates
110 (13%) malaria positive
1 (6%) isolates co-infected with malaria
0 (0%) NTS isolates
0 (0%) NTS-malaria co-infection
3 (19%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
12 (75%) Gram-positive isolates
1 (100%) Gram-positive-malaria co-infection
0 (0%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
Ghana
Asante Akim North (AAN)
1 H (IPD)
2651 febrile patients recruited
2651 (100%) blood culture performed
2651 (100%) malaria test performed
157 (6%) culture positive isolates
1139 (43%) malaria positive
13 (8%) isolates co-infected with malaria
46 (29%) NTS isolates
6 (46%) NTS-malaria co-infection
32 (20%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
53 (34%) Gram-positive isolates
7 (54%) Gram-positive-malaria co-infection
26 (17%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
Guinea-Bissau (GB)
Bissau
1 H, 1 HC (IPD/OPD)
1021 febrile patients recruited
1021 (100%) blood culture performed
525 (51%) malaria test performed
30 (3%) culture positive isolates
206 (39%) malaria positive
4 (13%) isolates co-infected with malaria
7 (23%) NTS isolates
3 (75%) NTS-malaria co-infection
3 (10%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
16 (53%) Gram-positive isolates
1 (25%) Gram-positive-malaria co-infection
4 (13%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
Kenya
Kibera
1 HC (OPD)
1251 febrile patients recruited
1251 (100%) blood culture performed
956 (76%) malaria test performed
107 (9%) culture positive isolates
226 (24%) malaria positive
11 (10%) isolates co-infected with malaria
6 (6%) NTS isolates
1 (9%) NTS-malaria co-infection
54 (50%) S. Typhi isolates
3 (27%) S.Typhi-malaria co-infection
43 (40%) Gram-positive isolates
7 (64%) Gram-positive-malaria co-infection
4 (4%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection

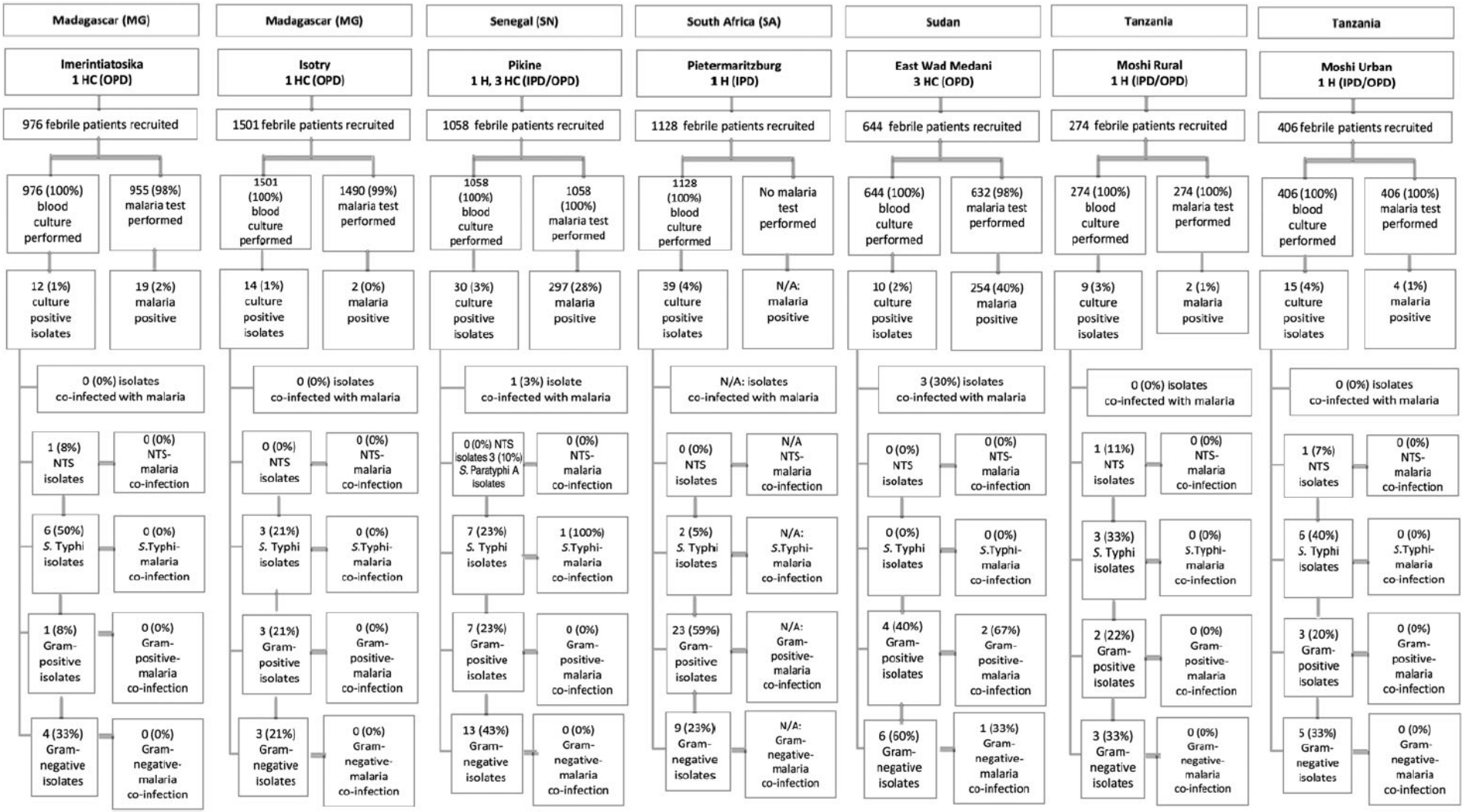

Madagascar (MG)
Imerintiatosika
1 HC (OPD)
976 febrile patients recruited
976 (100%) blood culture performed
955 (98%) malaria test performed
12 (1%) culture positive isolates
19 (2%) malaria positive
0 (0%) isolates co-infected with malaria
1 (8%) NTS isolates
0 (0%) NTS-malaria co-infection
6 (50%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
1 (8%) Gram-positive isolates
0 (0%) Gram-positive-malaria co-infection
4 (33%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
Madagascar (MG)
Isotry
1 HC (OPD)
1501 febrile patients recruited
1501 (100%) blood culture performed
1490 (99%) malaria test performed
14 (1%) culture positive isolates
2 (0%) malaria positive
0 (0%) isolates co-infected with malaria
0 (0%) NTS isolates
0 (0%) NTS-malaria co-infection
3 (21%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
3 (21%) Gram-positive isolates
0 (0%) Gram-positive-malaria co-infection
3 (21%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
Senegal (SN)
Pikine
1 H, 3 HC (IPD/OPD)
1058 febrile patients recruited
1058 (100%) blood culture performed
1058 (100%) malaria test performed
30 (3%) culture positive isolates
297 (28%) malaria positive
1 (3%) isolate co-infected with malaria
0 (0%) NTS isolates 3 (10%) S. Paratyphi A isolates
0 (0%) NTS-malaria co-infection
7 (23%) S. Typhi isolates
1 (100%) S.Typhi-malaria co-infection
7 (23%) Gram-positive isolates
0 (0%) Gram-positive-malaria co-infection
13 (43%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
South Africa (SA)
Pietermaritzburg
1 H (IPD)
1128 febrile patients recruited
1128 (100%) blood culture performed
No malaria test performed
39 (4%) culture positive isolates
N/A: malaria positive
N/A: isolates co-infected with malaria
0 (0%) NTS isolates
N/A NTS-malaria co-infection
2 (5%) S. Typhi isolates
N/A: S.Typhi-malaria co-infection
23 (59%) Gram-positive isolates
N/A: Gram-positive-malaria co-infection
9 (23%) Gram-negative isolates
N/A: Gram-negative-malaria co-infection
Sudan
East Wad Medani
3 HC (OPD)
644 febrile patients recruited
644 (100%) blood culture performed
632 (98%) malaria test performed
10 (2%) culture positive isolates
254 (40%) malaria positive
3 (30%) isolates co-infected with malaria
0 (0%) NTS isolates
0 (0%) NTS-malaria co-infection
0 (0%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
4 (40%) Gram-positive isolates
2 (67%) Gram-positive-malaria co-infection
6 (60%) Gram-negative isolates
1 (33%) Gram-negative-malaria co-infection
Tanzania
Moshi Rural
1 H (IPD/OPD)
274 febrile patients recruited
274 (100%) blood culture performed
274 (100%) malaria test performed
9 (3%) culture positive isolates
2 (1%) malaria positive
0 (0%) isolates co-infected with malaria
1 (11%) NTS isolates
0 (0%) NTS-malaria co-infection
3 (33%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
2 (22%) Gram-positive isolates
0 (0%) Gram-positive-malaria co-infection
3 (33%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection
Tanzania
Moshi Urban
1 H (IPD/OPD)
406 febrile patients recruited
406 (100%) blood culture performed
406 (100%) malaria test performed
15 (4%) culture positive isolates
4 (1%) malaria positive
0 (0%) isolates co-infected with malaria
1 (7%) NTS isolates
0 (0%) NTS-malaria co-infection
6 (40%) S. Typhi isolates
0 (0%) S.Typhi-malaria co-infection
3 (20%) Gram-positive isolates
0 (0%) Gram-positive-malaria co-infection
5 (33%) Gram-negative isolates
0 (0%) Gram-negative-malaria co-infection

Figure 3.1 Flowchart of TSAP blood culture and malaria test performance

Original legends (Park *et al.* 2016): "Blood culture-positive isolates: contaminants excluded. Gram-negative isolates: *Salmonella* species excluded. Malaria tests performed per site: Nioko, Burkina Faso (BF; thick/thin blood smears), Polesgo, BF (thick/thin blood smears), Butajira, Ethiopia (Rapid Diagnostic Test [RDT] and thick/thin blood smears, Asante Akim North District (AAN), Ghana (thick/thin blood smears), Bissau, Guinea-Bissau (GB; thick/thin blood smears), Kibera, Kenya (thick blood smear), Imerintsiatosika, Madagascar (MG; RDT and thick/thin blood smears), Isotry, MG (RDT and thick/thin blood smears), Pikine, Senegal (RDT if available and thick/thin blood smears), Pietermaritzburg, South Africa (SA; malaria-free zone: no malaria test performed), East Wad Medani (EWM), Sudan (thick/thin blood smears), Moshi Rural (MR), Tanzania thick/thin blood smears), and Moshi Urban (MU), Tanzania (thick/thin blood smears). Numerators and denominators for each percentages (%) in the flowchart (in descending order from top to bottom): % of blood culture performed of recruited patients; % of malaria test performed of recruited patients; % of blood culture positive isolates of blood culture performed; % of malaria parasite-positive cases of malaria test performed; % of bacterial isolates co-infected with malaria of blood culture-confirmed positive isolates; % of non-typhoidal *Salmonella* (NTS), *S.* Typhi, Gram-positive, and non-*Salmonella* gram-negative isolates of blood culture-confirmed positive isolates; % of isolates with NTS-malaria co-infection, *S.* Typhi-malaria co-infection, gram-positive-malaria co-infection, non-*Salmonella* Gram-negative-malaria co-infection of all bacterial isolates co-infected with malaria. Malaria species: 2801/3133 malaria positives confirmed with malaria species; 332/3133 missing data on malaria species; 2779/2801 *Plasmodium falciparum*; 20/2801 *Plasmodium malariae;* 2/2801 *Plasmodium ovale.* Malaria species confirmed per site listed below. Nioko, BF: 430/430 *P. falciparum*; Polesgo, BF: 444/444 *P. falciparum*. Butajira, Ethiopia: 26/110 *P. falciparum* and 84 missing data on malaria species. AAN, Ghana: 1111/1139 *P. falciparum*, 20/1139 *P. malariae*, 2/1139 *P. ovale*, and 6 missing data on malaria species. Bissau, GB: 196/206 *P. falciparum* and 10 missing data on malaria species. Kibera, Kenya: not available/226 (no data on malaria species). Imerintsiatosika, MG: 19/19 *P. falciparum*; Isotry, MG: 2/2 *P. falciparum*. Pikine, Senegal: 291/297 *P. falciparum*, and 6 missing data on malaria species. Pietermaritzburg, SA: No malaria test performed as the country is malaria-free. EWM, Sudan: 254/254 *P. falciparum*. MR, Tanzania: 2/2 *P. falciparum*; MU, Tanzania: 4/4 *P. falciparum.* Abbreviations: H, hospital; HC, health centre; IPD, inpatient department; NA, not available; OPD, outpatient department."

3.2.2 Age-stratified frequencies of organisms causing bacteremia and parasitemia

Of 3,133 positive malaria tests, 1,386 (44%) were from children aged <5 years. The proportion of malaria coinfection with any bacterial pathogen from all 13 sites was 11% (53/497); predominantly a Gram-positive bacterial coinfection with malaria (22/53; 42%), particularly *Staphylococcus aureus* (13/22; 59%) and *Streptococcus pneumoniae* (5/22; 23%), and iNTS-malaria coinfection (15/53; 28%), in comparison to non-*Salmonella* Gram-negative bacterial coinfection with malaria (7/53; 13%) that included *E. coli* (3/7; 43%) and *Pseudomonas aeruginosa* (2/7; 29%) (Figure 3.1 and Table 3.1). Malaria-iNTS coinfections were more common among children <5 years of age (11/20; 55%), particularly in those under 2 years of age (7/12; 58%), whereas all malaria-*S.* Typhi coinfections occurred in children >5 years of age.

Children between 5 and 15 years of age had the highest proportion of malaria-bacteria coinfection with a Gram-positive bacterium (11/22; 50%). Children <2 years of age showed the highest proportion of iNTS (35/126; 28% or 35/73; 48%) and Gram-positive bacterial infections (50/126; 40% or 50/179; 28%) compared with the other age groups (Table 3.1).

Table 3.1 Age-specific frequencies of organisms isolated from blood culture and malaria test

Blood culture confirmed organisms	All ages	0 to <2 y	2 to <5 y	5 to <15 y	≥15 y	Median Age Y (Q1-Q3)
Blood culture performed (No.)	13431	2843	2402	3355	4831	
All pathogenic bacteria (no., % of No.)	497 (4)	126 (4)	107 (4)	141 (4)	123 (3)	5 (1-14)
NTS including 3 *S.* Paratyphi A (no., % of all pathogenic bacteria)[1]	76 (15)	35 (28)	24 (22)	10 (7)	7 (6)	2 (1-3)
Salmonella Typhi (no., % of all pathogenic bacteria)	137 (28)	6 (5)	34 (32)	67 (48)	30 (24)	8 (4-14)
Gram-negative bacteria (no., % of all pathogenic bacteria)[2]	93 (19)	34 (27)	6 (6)	15 (11)	38 (31)	6 (2-14)
Gram-positive bacteria (no., % of all pathogenic bacteria)	179 (36)	50 (40)	42 (39)	47 (33)	40 (33)	4 (1-13)
Malaria test performed (No.)[3]	11421	2136	2031	3007	4247	
Malaria positive (no., % of No.)	3133 (27)	527 (25)	859 (42)	1083 (36)	664 (16)	6 (2-12)
Plasmodium falciparum (no., % of malaria positive)	2779 (89)	500 (95)	782 (91)	913 (84)	584 (88)	5 (2-12)
Plasmodium malariae (no., % of malaria positive)	20 (1)	5 (1)	8 (1)	7 (1)	0 (0)	4 (2-6)
Plasmodium ovale (no., % of malaria positive)	2 (0.1)	0 (0)	0 (0)	2 (0.2)	0 (0)	6 (6-6)
Malaria-bacterial co-infection (no., % of all pathogenic bacteraemia)	53 (11)	12 (10)	8 (7)	22 (16)	11 (9)	6 (2-11)
Malaria-NTS (no., % of co-infection)	15 (28)	7 (58)	4 (50)	4 (18)	0 (0)	2 (1-5)
Malaria-*S.* Typhi (no., % of co-infection)	9 (17)	0 (0)	0 (0)	5 (23)	4 (36)	9 (6-22)
Malaria-gram-negative (no., % of co-infection)[4]	7 (13)	1 (8)	1 (13)	2 (9)	3 (27)	5 (1-11)
Malaria-gram-positive (no., % of co-infection)[5]	22 (42)	4 (33)	3 (38)	11 (50)	4 (36)	7 (3-11)

Original legends (Park *et al.* 2016):
Abbreviation: NTS, non-typhoidal *Salmonella*.
[1] Total of 3 *S.* Paratyphi A and 73 NTS isolates: 38/73 (50%) *Salmonella* Typhimurium, 15 of 73 (20%) *Salmonella* Enteritidis, 10 of 73 (14%) *Salmonella* Dublin, and 10 of 73 (14%) other undetermined *Salmonella* serovars. The 3 *S.* Paratyphi A isolates were all female; 14, 20, and 25 years of age; none exhibited malaria co-infection.
[2] Gram-negative bacteria: *Salmonella* species excluded.
[3] Malaria test was performed through Rapid Diagnostic Test or/and blood film (thick and thin smears) (Figure 1). Of 11,421 blood samples screened for malaria, 3,133 (27%) resulted positive: 20 *P. malariae* and 2 *P. ovale* were from Asante Akim North, Ghana. Three hundred thirty-two malaria-positive cases missed data on malaria species. Except for these, all were *P. falciparum*.
[4] Malaria gram-negative co-infection (*Salmonella* species excluded): Of the 7 cases of malaria co-infection with gram-negative bacteria, 3 were *Escherichia coli* (all >15 years of age) and 2 *Pseudomonas aeruginosa* (one <2 years of age, one 5 to <15 years of age). No cases of malaria co-infection with *Klebsiella pneumoniae.*
[5] Malaria gram-positive co-infection: Of 22 cases of malaria co-infection with gram-positive bacteria, 59% (13/22) were *Staphylococcus aureus* (3 between 2 and <5 years, 6 between 5 and <15 years, and 4 aged ≥15 years) and 5 *Streptococcus pneumoniae* (2 under 2 years of age, 3 between 5 and <15 years of age).

3.2.3 The correlation of between iNTS disease and malaria

A strong linear correlation of malaria with iNTS across sites was identified (p=0.01; r=0.70) (Figure 3.2). Areas with a higher burden of malaria had a higher odds of iNTS disease compared with other bacterial infections (OR, 4.89; 95% confidence interval [CI], 1.61-14.90; p=0.005; GEE logistic regression) than areas with lower burden of malaria (Table 3.2). In these sites with low malaria prevalence, *E. coli* (14 isolates out of 24 non-*Salmonella* Gram-negative bacterial infections; 58%, and 14/105 blood culture confirmed real pathogen; 13%) was the next common Gram-negative pathogen detected following *S.* Typhi. *Streptococcus pneumoniae* (20/44; 45%) and *Staphylococcus aureus* (13/44; 30%) were the predominant Gram-positive bacterial infections in these sites (Table 3.2). In sites with high malaria prevalence, *E. coli* (22/69; 32%), *Klebsiella pneumonia* (18/69; 26%), and *Pseudomonas aeruginosa* (5/69; 7%) were the predominant non-*Salmonella* Gram-negative bacterial infections following *S.* Typhi and iNTS. *Staphylococcus aureus* (71/135; 53%) and *Streptococcus pneumoniae* (47/135; 35%) were the predominant pathogens among the Gram-positive bacterial infections detected in these sites as well. Furthermore, relative to non-iNTS infections, *Plasmodium* parasite positivity was positively associated with iNTS disease (OR, 2.44; 95% CI, 1.09-5.47; p=0.031; stratified univariate analysis; Table 3.3).

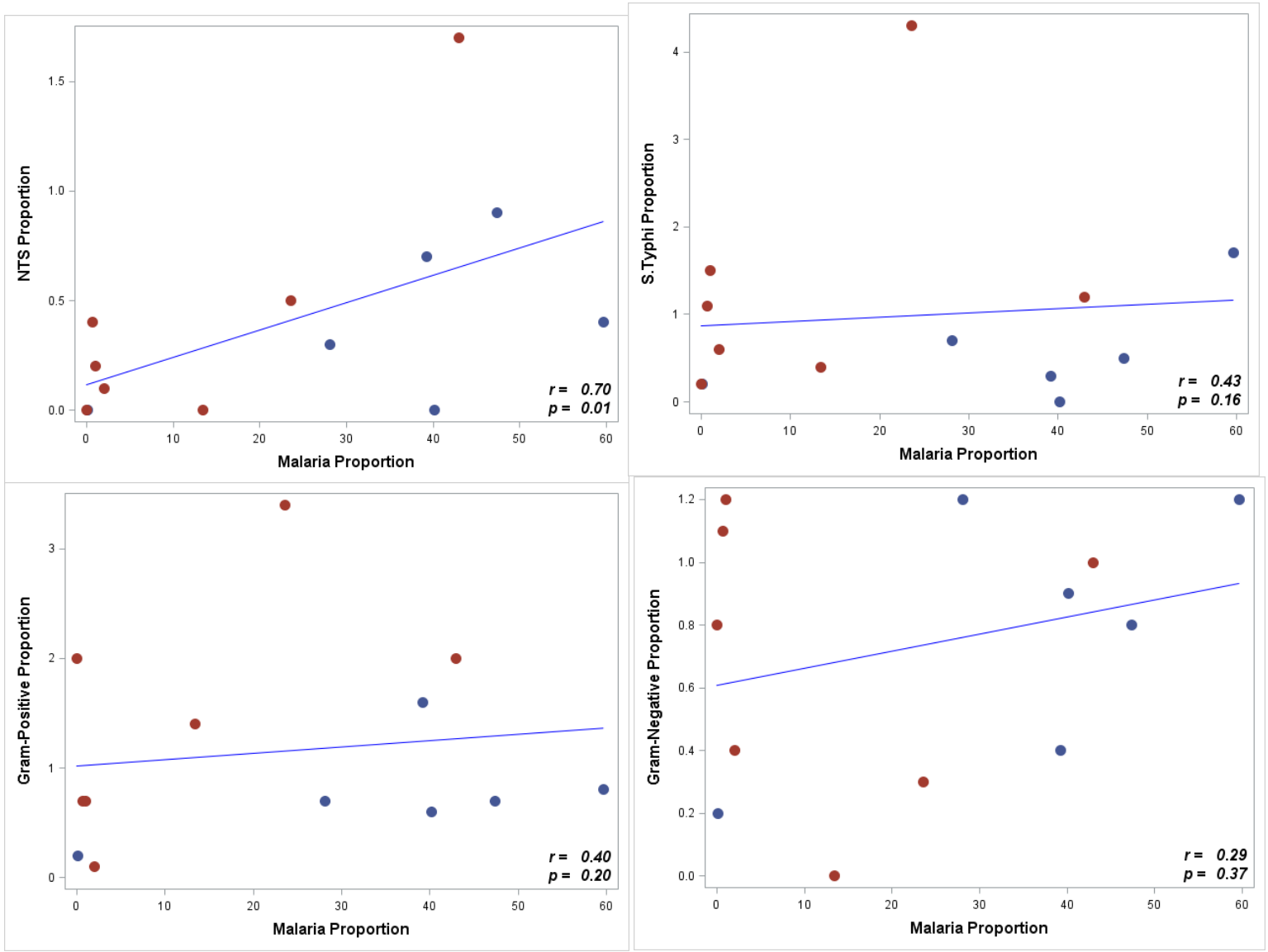


Figure 3.2 Correlation between frequency proportions of malaria and invasive nontyphoidal Salmonella (iNTS) compared to malaria with other invasive bacteria across 13 sites

Original legends (Park *et al.* 2016): "Spearman correlation coefficient (*r*) is analysed based on the proportion of frequencies of malaria, iNTS, *Salmonella* Typhi, Gram-positive and non-*Salmonella* Gram-negative bacterial isolates per site, controlled by each site study period. (Proportions of frequencies are calculated as iNTS, *S.* Typhi, gram-positive bacteria, non-*Salmonella* gram-negative bacteria positivity out of blood culture performed; malaria positivity out of malaria test performed.) Scattered dots represent each study sites. Frequencies of bacteraemia and *Plasmodium* parasite positivity per site are noted in Figure 1. Thirteen sites exhibited in the scattered dots are grouped per surveillance period below or above the median duration of surveillance period (20 months). Sites coloured in red dots are those with surveillance period of >20 months: Ethiopia, Ghana, Kenya, South Africa, and Tanzania (urban and rural). Sites coloured in blue dots are those with a surveillance period of ≤20 months: Burkina Faso (Nioko and Polesgo), Guinea-Bissau, Madagascar (Imerintsiatosika and Isotry), Senegal, and Sudan. Some sites with same or similar values may appear overlapped, but all 13 sites are dotted in the plot. 3 *S.* Paratyphi A isolates from Senegal are grouped under NTS in this analysis."

Table 3.2 The characteristics of bacterial infections in malaria endemic regions

Characteristic	Risk Factor (Exposure)			
	Sites With Lower Malaria Endemicity[1] (n[3] = 105) n (%)	Sites With Higher Malaria Endemicity[2] (n = 392) n (%)	Odds Ratio (95% CI)	*P Value*
iNTS infected[4]	3 (2.9)	73 (18.6)	4.89 (1.61-14.90)	0.005
Salmonella Typhi infection	23 (21.9)	114 (29.1)	0.94 (0.38-2.32)	0.893
Gram-positive bacterial infection	44 (41.9)	135 (34.4)	0.76 (0.31-1.84)	0.540
Gram-negative bacterial infection[5]	24 (22.9)	69 (17.6)	1.09 (0.48-2.46)	0.842
Malaria co-infection with all bacteraemia[6]	1 (1.5)	52 (14.6)	17.44 (2.76-110.10)	0.002

Original legends (Park *et al.* 2016):

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CI, confidence interval; iNTS, invasive non-typhoidal *Salmonella*.

[1] Sites with lower malaria endemicity (lower-frequency proportions of malaria): Ethiopia (Butajira), Madagascar (Imerintsiatosika, Isotry), Tanzania (Moshi Rural, Moshi Urban), and malaria-free South Africa (Pietermaritzburg) (see Figure 1).

[2] Sites with higher malaria endemicity (higher-frequency proportions of malaria): Burkina Faso (Nioko, Polesgo), Ghana (Asante Akim North District), Guinea-Bissau (Bissau), Kenya (Kibera), Senegal (Pikine), and Sudan (East Wad Medani) (see Figure 1).

[3] No. = blood culture-confirmed real pathogen (excluding contaminants).

[4] iNTS infection: 3 *S.* Paratyphi A isolates grouped under iNTS in this analysis.

[5] Gram-negative bacterial infections excluding *Salmonella* spp.

[6] Malaria co-infection with all bacteraemia is analysed based on number of blood culture positive cases with malaria test performed. Out of total 497 blood culture positive isolates, 422 had malaria test performed, which is grouped into sites with lower malaria endemicity (*n*=65) and sites with higher malaria endemicity (*n*=357).

3.2.4 The clinical characteristics of iNTS disease

Patients with severe anaemia (haemoglobin level <7 g/dL for age group 0 to <5 years; <8 g/dL for ≥5 years) had >10 times higher odds of iNTS disease (univariate analysis: OR, 13.10; $p<0.0001$; multivariable analysis: OR, 14.62; $P<0.0001$) than non-iNTS bacteremia. Moderate anaemia was also associated with iNTS disease (Table 3.3). Among 76 iNTS patients, including 3 *S.* Paratyphi A cases, 34 (45%) had severe anaemia and 10 (15%) iNTS patients <10 years of age were severely underweight. iNTS patients exhibited the highest proportion of hospitalization (54/76; 71%) and diarrhea (22/76; 29%) compared to those with other bacteremia: 32% (44/137) and 24% (33/137) of patients infected with *S.* Typhi; 54% (96/179) and 16% (29/179) of patients with Gram-positive bacterial infections; and 56% (52/93) and 16% (15/93) of patients with non-*Salmonella* Gram-negative bacterial infections were hospitalized and had diarrhea.

Table 3.3 Univariate and multivariable analyses of characteristics associated with iNTS disease

Characteristics Associated With iNTS Disease	Univariate Analysis[1]				Multivariable Analysis	
	iNTS (n^2 = 76)	Non-NTS bacteraemia (n^3 = 421)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Malaria parasite positivity	15 (19.7)	38 (9.0)	2.44 (1.09-5.47)	0.031	2.10 (0.84-5.24)	0.110
Nutritional status[4]						
Moderate underweight (<10 y)[5]	8 (11.9)	30 (12.0)	1.05 (0.43-2.54)	0.917	NA[6]	NA[6]
Severe underweight (<10 y)[7]	10 (14.9)	47 (18.9)	0.96 (0.43-2.14)	0.919	NA[6]	NA[6]
Anaemia status [8]						
Moderate anaemia [9]	27 (35.5)	65 (15.4)	6.99 (2.79-17.52)	<.0001	6.05 (2.41-15.21)	0.0001
Severe anaemia [10]	34 (44.7)	69 (16.4)	13.10 (5.05-33.97)	<.0001	14.62 (5.56-38.43)	<.0001

Original legends (Park *et al.* 2016):
Data are presented as No. (%) unless otherwise specified. Abbreviations: CI, confidence interval; iNTS, invasive non-typhoidal *Salmonella*; NA, not applicable; NTS, non-typhoidal *Salmonella*; OR, odds ratio; SD, standard deviation.
[1] Stratified logistic regression was used for this univariate and multivariable analysis.
[2] Total valid case number (n) for iNTS includes the 3 *S.* Paratyphi A cases for this analysis.
[3] Total valid case number (n) for non-NTS bacteraemia is the total number of blood culture positives (497) minus total number of NTS isolates (976 including 3 *S.* Paratyphi A): n=421.
[4] Association between malnutrition (moderate and severe underweight) and iNTS disease compared to non-iNTS bacteraemia. Both moderate and severe underweight cases compared with those without malnutrition.
[5] Total valid case number (No.) for moderate underweight cases for patients <10 years of age: NTS (n=8), non-NTS bacteraemia (n=30). World Health Organization (WHO) Global Database on Child Growth and Malnutrition: z score cut-off point of < -2 SD and > -3 SD to classify moderate under nutrition.
[6] Not applicable due to missing data for patients >10 years of age.
[7] Total valid case number (No.) for severe underweight cases for patients <10 years of age: NTS (n=10), non-NTS bacteraemia (n=47). WHO Global Database on Child Growth and Malnutrition: z score cut-off point of < -3 SD to classify severe under nutrition.
[8] Association between anaemia (moderate and severe anaemia) and iNTS disease compared to non-iNTS bacteraemia. Both moderate and severe anaemia cases compared with those without anaemia.
[9] Moderate anaemia: age group 0 to <5 years with haemoglobin level 7-9.9 g/dL, and age group ≥5 years with haemoglobin level 8-10.9 g/dL. Definition based on the World Health Organisation report on "Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity" (World Health Organisation 2011).
[10] Severe anaemia: age group 0 to <5 years with haemoglobin level <7 g/dL, and age group ≥5 years with haemoglobin level <8 g/dL (World Health Organisation 2011).

3.3 Discussion

Here I identified a positive correlation between malaria and iNTS in multiple countries in sub-Saharan Africa. Further, iNTS disease and Gram-positive bacteraemia were the most common malarial/bacterial coinfections in these areas, exceeding the number of coinfections with *S.* Typhi and non-*Salmonella* Gram-negative bacteraemia. However, some of the sites (East Wad Medani, Sudan and Kibera, Kenya) did not follow this trend as they had a low level of iNTS infections despite a high burden of malaria. This lack of association may be associated with a low local level of transmission of iNTS disease, leading to reduced exposure of children with malaria to iNTS organisms. The patterns of iNTS and malaria infections should also be further investigated in the context of the travel history of Kibera residents or rural-urban migration to Kibera, as people residing in Kibera travel within Kenya and their malaria infections may be associated with travel to areas with a higher malaria risk (Njuguna *et al.* 2016).

My data support the finding of previous studies (Scott *et al.* 2011; Mackenzie *et al.* 2010; Krumkamp *et al.* 2016) that identified an association between iNTS disease and *Plasmodium* parasite-positive individuals. I additionally found a high proportion of Gram-positive bacterial coinfections with malaria, contrasting earlier studies from the Gambia (Mabey, Brown and Greenwood 1987) and Malawi (Bronzan *et al.* 2007), that showed a strong association between malaria and iNTS disease, but little evidence for any association between malaria and non-*Salmonella* bacteraemia. However, a recent meta-analysis of studies of children with severe malaria and bacteraemia (Church and Maitland 2014) indicated that the overall prevalence of Gram-positive organisms in children with malaria was greater than that of Gram-negative organisms with *Staphylococcus aureus*, which was the main pathogen isolated in 3 studies. This

observation is consistent with malaria-induced impairment of neutrophil function as an underlying causal link: Patients with chronic granulomatous disease, a congenital defect of neutrophil oxidative burst, are particularly susceptible to invasive *S. aureus* and *Salmonella* infections (Mouy *et al.* 1989). However, a recent study in Malawi suggested a significant association between only gram-negative and malaria-protective phenotype of sickle-cell trait (HbAS) (Scott *et al.* 2011), warranting the needs for more research on the associations between malaria and other Gram-negative bacteremia as well as Gram-positive bacteremia.

Although further investigation is required to understand the temporal precedence of infections with malaria parasites and iNTS for a risk factor analysis for iNTS disease (including the association between iNTS disease and recent malaria vis-à-vis current malaria or malaria parasite density) (Scott *et al.* 2011; Mackenzie *et al.* 2010; Biggs *et al.* 2014) a multitude of potential mechanisms may explain this observation. Malaria impairs the oxidative burst function of macrophages and neutrophils, which is likely to increase the risk for iNTS disease, as oxidative burst is key for eliminating *Salmonella* from the intracellular niches (Vazquez-Torres *et al.* 2000; Winklestein *et al.* 2000; Gondwe *et al.* 2010; Schwarzer *et al.* 1992). More recently, the association between malaria and iNTS has been linked to induction of heme oxygenase-1 (HO-1) in a mouse model of malaria that made animals more susceptible to NTS infection (Cunnington *et al.* 2011). The same researchers demonstrated that impaired neutrophil oxidative burst was associated with HO-1 induction in Gambian children with malaria (Cunnington *et al.* 2012). Malaria has also been shown to increase susceptibility to NTS infection in the mice through inhibition of IL-12 (Roux *et al.* 2010) and increased IL-10 (Lokken *et al.* 2014). The precise contribution of this HO-1 pathway mechanism to enhanced

susceptibility to iNTS disease in humans needs to be further investigated.

The study has limitations. First, the surveillance period was not long enough to investigate any potential seasonality of malaria, iNTS disease, and coinfections. Second, given that individuals with mild cases of malaria do not necessarily seek healthcare at hospitals, the true burden of malaria is likely to be underreported. Different malaria diagnostics may have also influenced the rate of malaria detection (Harchut *et al.* 2013), and I was unable to distinguish current from recent malaria in my analysis of iNTS risk factors. Third, HIV testing was not performed, as HIV seroprevalence was not a main objective of this study. Insufficient clinical data precluded the development of robust clinical diagnostic criteria to better predict the causative agents of the patients and the cause of fever, although diarrhea was indicative of iNTS.

This standardized multicentre surveillance approach contributes additional information on the epidemiology of iNTS disease and malaria in Africa. The positive association between malaria and iNTS disease support the role of NTS as a common aetiology of invasive bacterial disease among children with malaria in areas where malaria is highly prevalent. Furthermore, given that two to several days may be required to confirm bacteraemia microbiologically (Mancini *et al.* 2010), patients with febrile symptoms commonly are given antimalarials and antibacterials simultaneously, rendering them prone to developing AMR. A similar scenario has occurred with *P. falciparum*, which is already resistant to chloroquine and sulfadoxine-pyrimethamine in most parts of sub-Saharan Africa, and potentially to artemisinin derivatives in the future (Plowe 2009). A high burden of iNTS disease and malaria, coupled with increasing AMR (Walsh *et al.* 2000; Lunguya *et al.* 2013) may potentially contribute to increased severity of illness.

This provides additional evidence to prioritize the development of an iNTS vaccine, specifically designed for the African setting and used in areas of high iNTS prevalence and malaria endemicity. Such a vaccine could either be developed in a single formulation as a bivalent *Salmonella* Typhimurium and *Salmonella* Enteritidis regimen, given their predominance in sub-Saharan Africa as also found in my study, or as a trivalent compound, including *Salmonella* Typhi. Irrespective, surveillance for bacterial bloodstream infections to identify prevalent isolates should continue to monitor emerging pathogens and AMR. Further research on the development of rapid and accurate diagnostics of invasive *Salmonella* infections to minimize the risk of unnecessary simultaneous exposure to both antibiotics and antimalarials for those febrile patients is also warranted.

Chapter 4 The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa

All work described in Chapter 4 has been published in the journal of Nature Communications during my DPhil (See Chapter 9) (Park *et al.* 2018).

4.1 Abstract

There is paucity of data regarding the geographical distribution, incidence, and phylogenetics of multi-drug resistant (MDR) *S.* Typhi in sub-Saharan Africa. Here I present a phylogenetic reconstruction of whole genome sequenced 249 contemporaneous *S.* Typhi isolated between 2008-2015 in 11 sub-Saharan African countries, in context of the 2,057 global *S.* Typhi genomic framework. Despite the broad genetic diversity, the majority of organisms (225/249; 90%) belonged to only three genotypes, 4.3.1 (H58) (99/249; 40%), 3.1.1 (97/249; 39%), and 2.3.2 (29/249; 12%). Genotypes 4.3.1 and 3.1.1 were found to be confined within East and West Africa, respectively. MDR phenotype was found in >50% of organisms and restricted within these two dominant genotypes. I identified a high incidence of MDR *S.* Typhi in locations with a high burden of typhoid, specifically in children aged <15 years. Antimicrobial stewardship, MDR surveillance, and the introduction of typhoid conjugate vaccines will be critical for the control of MDR typhoid in Africa.

4.2 Introduction

Typhoid fever, caused by *S.* Typhi and associated with systemic infection, is one of the most common community acquired bacteraemia in LMICs, the disease is particularly

common in sub-Saharan Africa (Marks *et al.* 2017) and South Asia. Increasing concerns on the effect of existing antimicrobials for typhoid patient treatment have been reported over the last decades as *S.* Typhi that exhibit resistance to empirical antimicrobials hamper successful therapy (Thanh *et al.* 2016). The phenomenon of AMR and MDR to the traditional first-line antimicrobials, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (co-trimoxazole) in *S.* Typhi was associated with large outbreaks in Asia in the 1980s and 1990s (Rowe, Ward and Threlfall 1997; Mirza, Beeching and Hart 1996). The emergence of resistance to these first line antimicrobials in Asia, which was dominated by the *S.* Typhi haplotype 58 (H58; renamed genotype 4.3.1) (Roumagnac *et al.* 2006; Holt *et al.* 2011), led to a change in typhoid treatment guidelines, with fluoroquinolones becoming the empirical choice for MDR infections (Akhtar *et al.* 2015; Emary *et al.* 2012). However, this shift towards the more common use of fluoroquinolones was inevitably followed by a decline in susceptibility to this group of antimicrobials (Thanh *et al.* 2016; Parry 2003).

Recent phylogenetic analyses found that the MDR *S.* Typhi genotype 4.3.1 dominates and circulates across Southeast (lineage I: Vietnam, Cambodia, and Laos) and South Asia (lineage II: mostly India with clusters in Nepal and Pakistan) (Wong *et al.* 2015). Additionally, these 4.3.1 *S.* Typhi have transferred from South Asia into Eastern and Southern Africa (lineages I and II; Kenya, Tanzania, Malawi, South Africa) (Wong *et al.* 2015; Feasey *et al.* 2015; Kariuki *et al.* 2010). The characteristics of 4.3.1 *S.* Typhi define this genotype as a key driving force in global MDR *S.* Typhi, as intercontinental transmission, regional circulation, and multiple localised outbreaks over the last three decades are distinct from the evolutionary trends and population structure of other extent *S.* Typhi genotypes (Wong *et al.* 2015; Wong *et al.* 2016a). Despite the known

circulation of 4.3.1 *S.* Typhi in sub-Saharan Africa, there is a paucity of data regarding the geographical distribution of AMR genotypes (MDR and reduced susceptibility to fluoroquinolones), their phylogenetic structure, and the incidence of MDR typhoid fever across the African continent.

Here, using 249 *S.* Typhi isolates confirmed from 11 African countries, I investigated the phylogeography and incidence of MDR typhoid fever across sub-Saharan Africa. This collection included 135 *S.* Typhi isolates blood-cultured from 13,431 febrile patients who participated in multi-country typhoid fever surveillance across ten countries in sub-Saharan Africa (Burkina Faso, Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, Sudan (no *S.* Typhi detected), and Tanzania) (Marks *et al.* 2017; Von Kalckreuth *et al.* 2016) and additional 114 *S.* Typhi from other typhoid fever studies implemented in Ghana, Uganda, and The Gambia.

4.3 Results

4.3.1 The geographical distribution of *Salmonella* Typhi genotypes in Africa

Phylogenetic analysis of 249 contemporary African *S.* Typhi genome sequences combined with 2,057 existing *S.* Typhi genome sequences (including 504 from Africa) permitted a visualisation of these new African isolates within a global *S.* Typhi genomic framework (Figure 4.1). The primary observation was that these 249 contemporary African *S.* Typhi sequences were distributed throughout this framework, with multiple lineages found to be circulating simultaneously across sub-Saharan Africa in the last decade. With TSAP providing expansive sampling across the continent, I observed a substantial degree of genetic diversity, with 12 different *S.* Typhi genotypes represented in 11 different typhoid endemic countries (Figure 4.2). This distribution of genotypes

ranged from single organisms in some countries (e.g. The Gambia, Kenya, and Uganda) to numerous closely related organism clusters isolated in several countries (Table 4.1).

Despite the apparent broad genetic diversity in the circulating *S*. Typhi population, the majority of the recently isolated organisms (225/249; 90%) belonged to only three genotypes, 4.3.1 (H58) (99/249; 40%), 3.1.1 (97/249; 39%), and 2.3.2 (29/249; 12%). Organisms belonging to genotype 4.3.1 were found in East Africa only, comprising 100% of the *S*. Typhi isolates from Kenya (59/59) and Uganda (30/30), and 91% (10/11) of the isolates from Tanzania (Figure 4.1 and Figure 4.2). Conversely, all of the organisms belonging to genotype 3.1.1 were found only in West African sites, constituting 88% (89/101) and 57% (8/14) of the *S*. Typhi organisms sequenced from Ghana and Burkina Faso, respectively. Organisms belonging to genotype 2.3.2 were found only in the West African countries of Burkina Faso, The Gambia, Ghana, Guinea-Bissau, and Senegal (Figure 4.2 and Table 4.1).

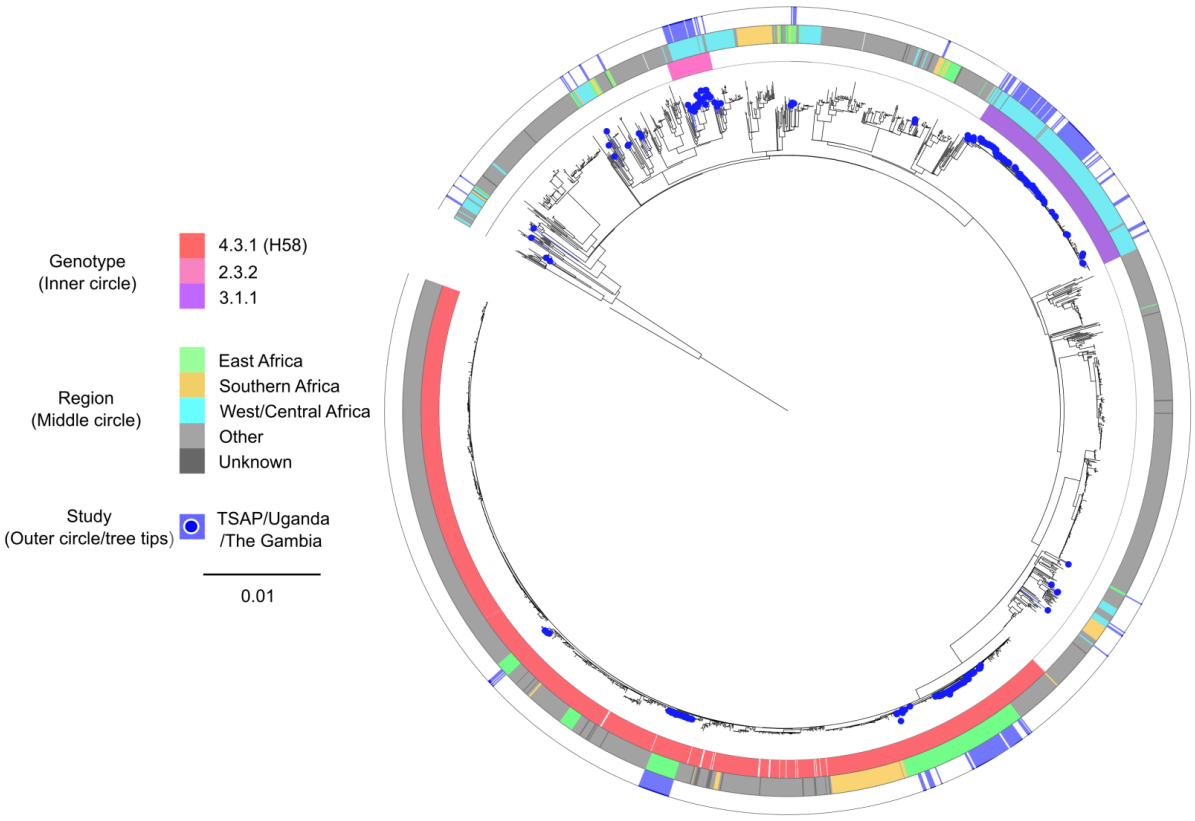


Figure 4.1 The phylogenetic context of *Salmonella* Typhi isolated in sub-Saharan Africa

Original legend (Park *et al.* 2018): "Maximum likelihood tree outlining the phylogenetic structure of 249 *S.* Typhi isolates unique to this study (highlighted by the blue points) combined with 2,057 global *S.* Typhi isolates. The tree is adjacent to three concentric circles highlighting associated metadata: The inner most circle represents the three most predominant genotypes (colour coded according to top of key), the middle circle represents the geographical sub-regions of Africa from where the *S.* Typhi organisms were isolated (colour coded according to top of key), and the outer circle (blue) again highlights the organisms unique to this study. The scale bar indicates the number of substitutions per variable site."

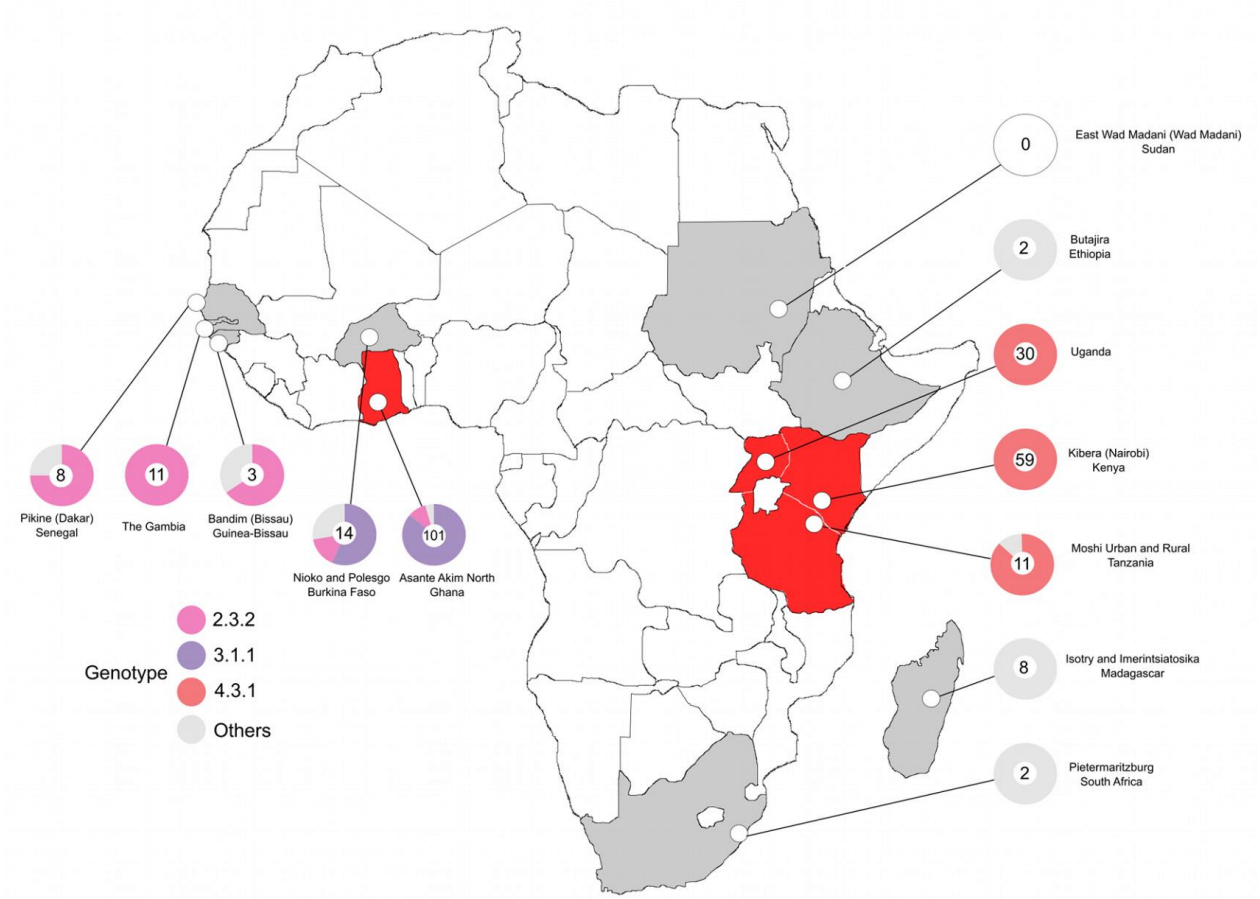


Figure 4.2 The distribution of multi-drug resistant *Salmonella* Typhi isolated in Africa

Original legends (Park *et al.* 2018): "Map of the African continent showing the locations of the field sites from where the *S.* Typhi organisms were isolated for this study. Countries in which multi-drug resistance (MDR) *S.* Typhi were isolated are coloured in red, countries in which MDR *S.* Typhi were not isolated are coloured in grey. Pie charts correspond with the proportion of the main genotypes isolated (see key), with the number of isolates from each location in the centre."

Table 4.1 The distribution of major MDR *S.* Typhi genotypes circulating in sub-Saharan Africa

Original legend (Park *et al.* 2018):

Country (total no. of *S.* Typhi)	Genotypes	No. of *S.* Typhi	% of total no. of *S.* Typhi per country
Burkina Faso (14)	2.2	2	14
	2.3.2	2	14
	3.1.1	8	57
	4.1.1	2	14
Ethiopia (2)	1.2	1	50
	2.2.2	1	50
Gambia (11)	2.3.2	11	100
Ghana (101)	0.0.1	1	1
	0.0.3	2	2
	2.3.2	8	8
	3.1.1	89	88
	4.1	1	1
Guinea-Bissau (3)	2.3.1	1	33
	2.3.2	2	67
Kenya (59)	4.3.1	59	100
Madagascar (8)	2.2	3	38
	2.5	4	50
	4.1	1	13
Senegal (8)	2.3.2	6	75
	3.1	1	13
	4.1	1	13
South Africa (2)	3.3.1	2	100
Tanzania (11)	2.2.2	1	9
	4.3.1	10	91
Uganda (30)	4.3.1	30	100

Genotypes (number of isolates)	Region	Country	Genotype per country	MDR[1] per country
4.3.1 (99)	East Africa	Kenya (n=59)	60% (59/99)	85% (50/59)
		Uganda (n=30)	30% (30/99)	23% (7/30)
		Tanzania (n=10)	10% (10/99)	40% (4/10)
3.1.1 (97)	West Africa	Ghana (n=89)	92% (89/97)	76% (68/89)
		Burkina Faso (n=8)	8% (8/97)	0% (0/8)
2.3.2 (29)	West Africa	Gambia (n=11)	38% (11/29)	0%
		Ghana (n=8)	28% (8/29)	0%
		Senegal (n=6)	21% (6/29)	0%
		Burkina Faso (n=2)	7% (2/29)	0%
		Guinea Bissau (n=2)	7% (2/29)	0%

Genotype	Number of isolates	MDR (%) per genotype
4.3.1 (H58)	99 (40%)	62% (61/99)
3.1.1	97 (39%)	70% (68/97)
2.3.2	29 (12%)	0%
Other minor genotypes[2]	24 (10%)	0%
Total	**249 (100%)**	**52% (129/249)**

[1] MDR definition used for the analysis: presence of resistant genes for at least one agent in all three antimicrobial categories listed below (detected in this study)

- Ampicillin/amoxicillin: beta-lactamase (*OXA-1, TEM-95/-93*)
- Chloramphenicol: (*catA1*)
- Trimethoprim-sulfamethoxazole: sulfonamide (*sul1, sul2*) and trimethoprim (*dfrA7, dfrA14, dfrA15*)

[2] Other minor genotypes of *S.* Typhi organisms (genotype distribution per country):

- 2.2 Total 7 S. Typhi: 1/2 (50%) Ethiopia, 3/8 (38%) Madagascar, 2/14 (14%) Burkina Faso, 1/11 (9%) Tanzania
- 4.1.1 Total 5 S. Typhi: 2/14 (14%) Burkina Faso, 1/8 (13%) Senegal, 1/8 (13%) Madagascar, 1/101 (1%) Ghana
- 2.5 Total 4 S. Typhi: 4/8 (50%) Madagascar
- 3.3.1 Total 2 S. Typhi: 2/2 (100%) South Africa
- 0.0.3 Total 2 S. Typhi: 2/101 (2%) Ghana
- 1.2 Total 1 S. Typhi: 1/2 (50%) Ethiopia
- 2.3.1 Total 1 S. Typhi: 1/3 (33%) Guinea-Bissau
- 3.1 Total 1 S. Typhi: 1/8 (13%) Senegal
- 0.0.1 Total 1 S. Typhi: 1/101 (1%) Ghana

4.3.2 MDR phenotypes and dominant *Salmonella* Typhi genotypes

An MDR phenotype was prevalent across isolates from the 11 sampled countries, with 129/249 (52%) of all isolates exhibiting the classical *S.* Typhi MDR phenotypic profile of resistance against ampicillin, chloramphenicol, and co-trimoxazole. MDR organisms were widely distributed in both East and West Africa, and isolated in Ghana (68/101; 67%), Kenya (50/59; 85%), Tanzania (4/11; 36%), and Uganda (7/30; 23%). No MDR organisms were identified in Burkina Faso (0/14), Ethiopia (0/2), The Gambia (0/11), Guinea-Bissau (0/3), Madagascar (0/8), Senegal (0/8), or South Africa (0/2). None of the organisms in these countries were genotype 4.3.1 or 3.1.1 except for Burkina Faso (8/14; genotype 3.1.1) (Figure 4.2 and Table 4.2).

Saliently, MDR phenotypes were confined entirely within the dominant circulating genotypes in East (4.3.1) and West Africa (3.1.1). Overall, 70% (68/97) of 3.1.1 *S.* Typhi and 62% (61/99) of 4.3.1 *S.* Typhi were MDR (Table 4.1). Further investigation revealed distinct origins of these MDR *S.* Typhi genotypes in each region. These contemporary genome sequences were compared to the existing global framework for *S.* Typhi 4.3.1 (Wong *et al.* 2015) using a maximum likelihood phylogeny (Figure 4.3a). The Kenyan MDR 4.3.1 organisms (2012-2013) belonged to two distinct clades, one in lineage I and the other in lineage II, indicative of the two distinct introductions from South Asia, as identified in an earlier global study (Wong *et al.* 2015), followed by the establishment of local populations. The Tanzanian MDR 4.3.1 organisms (2011-2012) clustered within each of these Kenyan clades, providing evidence of historical transfer of 4.3.1 *S.* Typhi from Kenya into Tanzania; ongoing local expansion was evident in the lineage I group only. The MDR 4.3.1 *S.* Typhi isolated in Uganda in 2015 formed a monophyletic clade within lineage II that was not closely related to the Kenyan or

Tanzanian lineage II organisms, and were characterised by extremely limited genetic diversity (mean pairwise genetic distance of 1 SNP), indicative of a recent population expansion or an outbreak (Kabwama *et al.* 2017). This Ugandan MDR cluster was nested within a clade of 4.3.1 MDR *S.* Typhi organisms isolated in South Asia between 2007 and 2011, consistent with a third importation of MDR *S.* Typhi into East Africa from South Asia (Figure 4.6a).

In contrast, the 3.1.1 MDR *S.* Typhi from Ghana (68 isolates) represented a population that was found only in West Africa, with the resulting phylogeny showing no evidence for inter-continental transmission as observed for 4.3.1 (Figure 4.6). Rather, 3.1.1 *S.* Typhi could be better defined as a repeating pattern of small country specific population expansions with organisms being regularly transferred between countries (Figure 4.6b).

Phylogeographical reconstruction has not previously been performed for *S.* Typhi 3.1.1, therefore I conducted a Bayesian spatio-temporal phylodynamics analysis for the subclade using BEAST2 (Figure 4.6b). First, I investigated the temporal structure in the data by using a root-to-tip regression and a date-randomisation test. My root-to-tip regression for the outgroup-rooted ML tree using TempEst exhibited a positive value for the slope (R^2 =0.12; *p*-value=3×10^{-6} in Figure 4.3). My date-randomisation test, with repeated analysis of 20 times while randomising the sampling times, displayed a strong temporal structure (Figure 4.4). Finally, my BEAST analysis using the uncorrelated lognormal clock and the exponential growth model exhibited an estimate of the time of origin of the 3.1.1 lineage (Figure 4.5).

The results suggest that Ghana was the most likely recent source of this 3.1.1 *S.* Typhi

population (posterior probability =0.66) which emerged *de novo*, and the corresponding source of three major clusters, which then radiated into other nearby countries on multiple occasions. Notably, Ghanaian *S.* Typhi appear to have been the probable origin of 3.1.1 *S.* Typhi in Burkina Faso on at least two separate occasions. Existing whole genome sequences of 131 *S.* Typhi from Nigeria, including two isolates from travellers returning to the United Kingdom from Nigeria, demonstrated that 3.1.1 *S.* Typhi has been introduced into Nigeria from Ghana on at least two separate occasions. One of these events, estimated to be between 2010 and 2011, formed a major population expansion (76/86; 88%) of the isolates from Nigeria.

Table 4.2 MDR and *gyrA S.* Typhi genotypes in four countries

Country (n, all *S.* Typhi per country)	MDR[1] *S.* Typhi (n)	MDR *S.* Typhi (%/out of all *S.* Typhi per country)	MDR *S.* Typhi Genotype	Non-susceptible to fluoroquinolones (n, *gyrA*)[2]
Ghana (101)	68	67	3.1.1	0
Kenya (59)	50	85	4.3.1 (H58)	9 (Ser83Phe)
Tanzania (11)	4	36	4.3.1 (H58)	0
Uganda (30)	7	23	4.3.1 (H58)	30 (Ser83Tyr)
Total 201 *S.* Typhi from 4 countries (out of 249 *S.* Typhi from 11 countries[3])	129	64% of 201 52% of 249		

Original legends (Park *et al.* 2018):

[1] MDR definition used for the analysis: presence of resistant genes for at least one agent in all three antimicrobial categories of ampicillin/amoxicillin (beta-lactamase: OXA-1, TEM-95/-93) AND chloramphenicol (*catA1*), AND trimethoprim-sulfamethoxazole (sulfonamide (*sul1, sul2*) and trimethoprim (*dfrA7, dfrA14, dfrA15*).

[2] Out of total 249 *S.* Typhi isolates yielded from this study in 11 countries in sub-Saharan Africa, total 39 isolates were non-susceptible to fluoroquinolone (ciprofloxacin and nalidixic acid (*gyrA*): 9 of 39 isolates were from Kenya, of which 7 were MDR *S.* Typhi; and all 30 isolates from Uganda were non-susceptible to fluoroquinolones, of which 7 were MDR *S.* Typhi. These 39 organisms exhibited the mutations at codon 83 of *gyrA*; serine (TCC) to phenylalanine (TTC) for all 9 isolates from Kenya (Ser83Phe) and serine (TCC) to TAC (tyrosine) for all 30 Uganda isolates (Ser83Tyr).

[3] No MDR *S.* Typhi from Burkina Faso (14; genotype 2.2 (2 isolates), 2.3.2 (2 isolates), 3.1.1 (8 isolates), 4.1.1 (2 isolates)), Ethiopia (2; genotypes 1.2 (1 isolate) and 2.2.2 (1 isolate)), Gambia (11 isolates, all genotype 2.3.2), Guinea-Bissau (3; genotypes 2.3.2 (2 isolates) and 2.3.1 (1 isolate), Madagascar (8; genotypes 2.5 (4 isolates), 2.2 (3 isolates), 4.1 (1 isolate)), Senegal (8; genotypes 2.3.2 (6 isolates), 3.1 (1 isolate), and 4.1 (1 isolate), and South Africa (2; all genotypes 3.1.1).

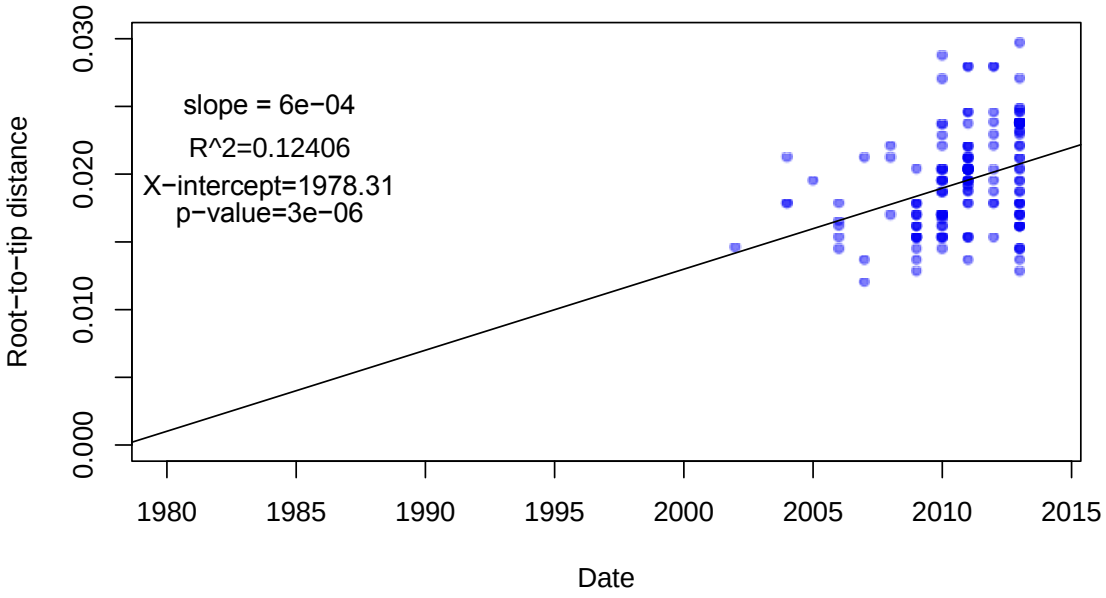


Figure 4.3 Root-to-tip regression for the subclade 3.1.1 maximum likelihood tree

Reproduced from Park *et al.* (2018). Original legend: "Each point on the plot corresponds to a measurement from the root to each tip in the tree. The solid line is the regression line fitted using the ordinary least squares method. The slope of the line is a crude estimate of the evolutionary rate, the x-intercept corresponds to the time to the most recent common ancestor, and the R^2 value measures the degree of clocklike behaviour. Note that the *y*-axis is the root-to-tip distance for the SNP alignment, such that the slope corresponds to the SNP rate estimate."

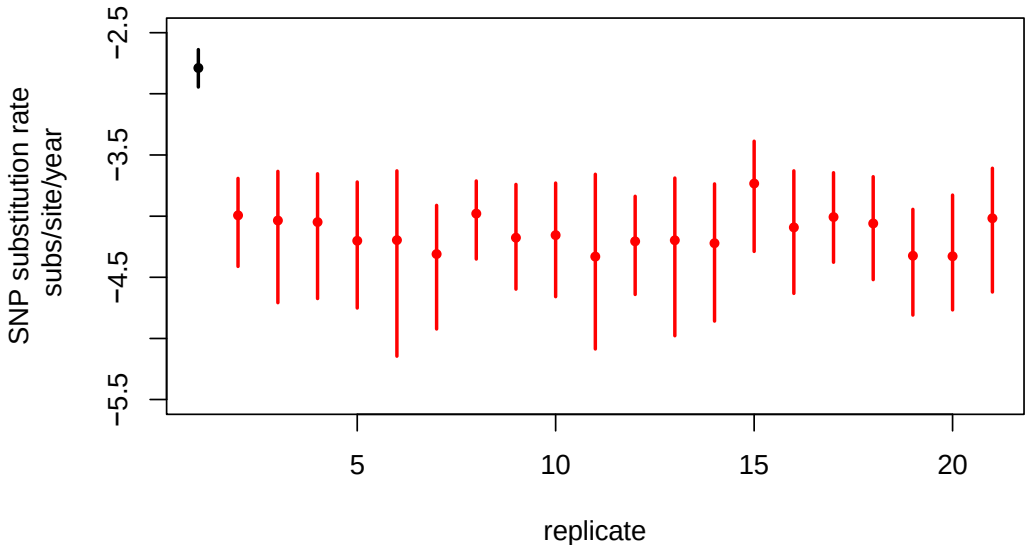


Figure 4.4 Date-randomization test for subclade 3.1.1 using BEAST2

Reproduced from Park *et al.* (2018). Original legend: "The *y*-axis shows the SNP evolutionary rate in $\log_{10}$ scale, while the *x*-axis shows the different replicates of the date-randomization test. Points are mean estimates and the lines are the Bayesian credible intervals around these values. The black symbol is for the data with real sampling times, while those in red are for the date-randomizations. The data are considered to display strong temporal structure if the estimate with the correct sampling times does not overlap with those from the randomizations."

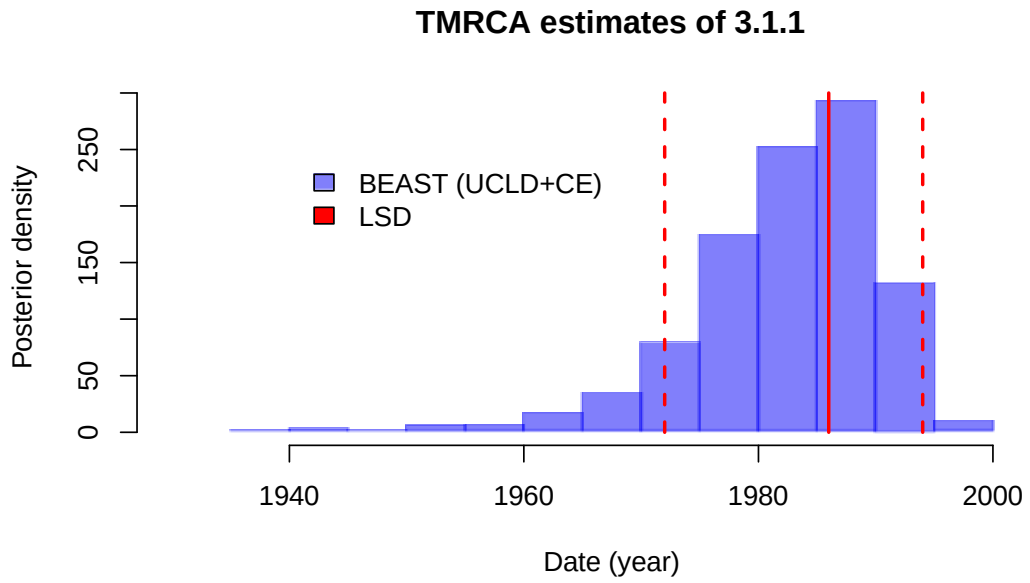


Figure 4.5 Estimates of the time to the most recent common ancestor of the 3.1.1 lineage using BEAST2 and LSD

Reproduced from Park *et al.* (2018). Original legend: "Blue histogram corresponds to the posterior distribution in BEAST2 using the uncorrelated lognormal clock model and the exponential growth coalescent tree prior. The red lines represent the estimate from LSD (Least-squares dating), where the solid line is the mean and the dashed lines are the 95% confidence interval."

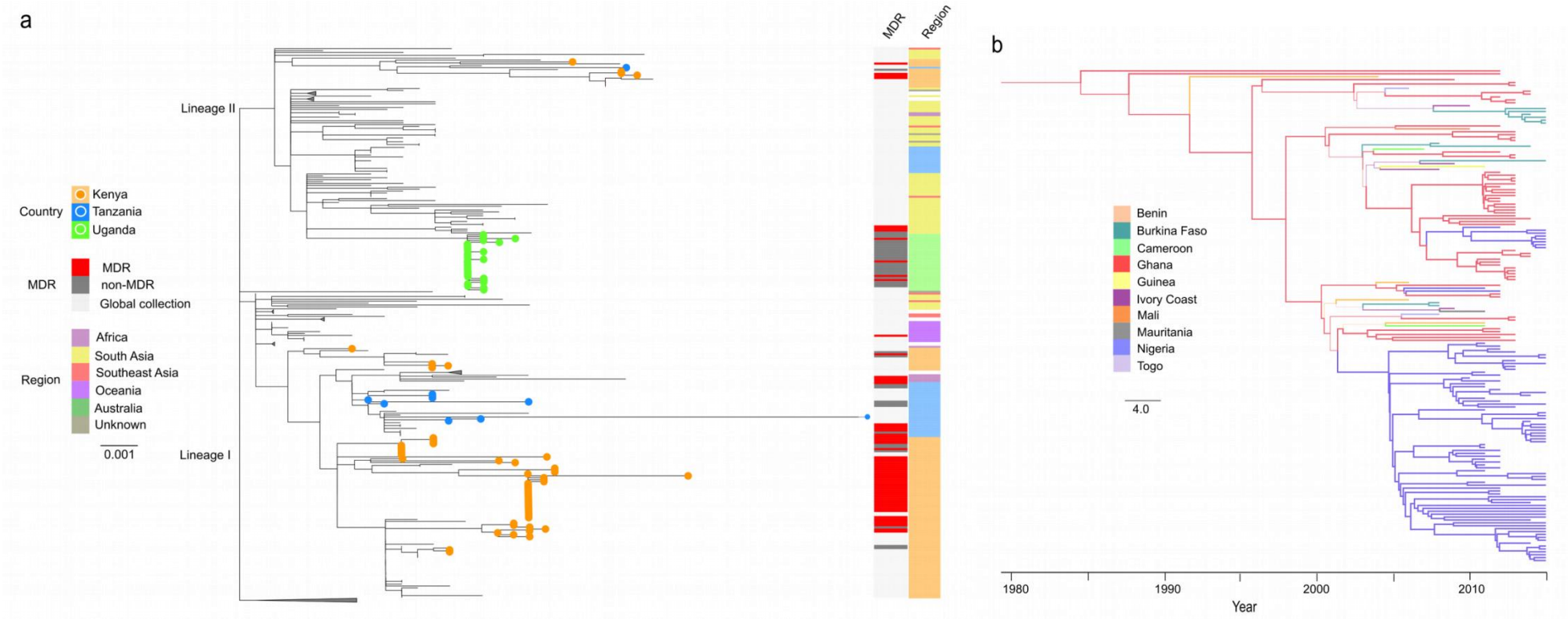


Figure 4.6 The phylogenetic structures of major *Salmonella* Typhi genotypes in sub-Saharan Africa

Original legend (Park *et al.* 2018): "**a)** Maximum likelihood tree of genotype 4.3.1 *S.* Typhi isolates from this study in the context of other global genotype 4.3.1 *S.* Typhi isolates; the two distinct sub-lineages are labeled at the base of the tree. 4.3.1 *S.* Typhi isolates from this study (Kenya, Tanzania, and Uganda) are highlighted in corresponding coloured branches and circles at the tip of each tree. The first coloured bar shows the MDR phenotypes of study isolates. The second coloured bar outlines the continents and African regions where 4.3.1 *S.* Typhi have been detected. Scale bar indicates the number of substitutions per variable site; nodes of the tree have been collapsed for better visualization. **b)** Maximum clade credibility tree (reconstructed using BEAST2) of genotype 3.1.1 *S.* Typhi isolates from this study in the context of other global genotype 3.1.1 *S.* Typhi isolates. Tree shows a phylogeographical reconstruction of genotype 3.1.1 *S.* Typhi isolates in West Africa. Branches are weighted by the support for the location changes; thicker branches have higher support. Branches and nodes are coloured according to the location that had the highest posterior probability values for some nodes of the tree. The scale bar indicates the number of substitutions per variable site per year."

4.3.3 Distinct IncHI1 MDR plasmids in East and West African *Salmonella* Typhi

I next investigated the genetic mechanisms associated with the MDR phenotypes by inferring AMR gene content in the 249 contemporaneous African *S.* Typhi genome sequences. Across the dataset I identified genes encoding resistance to aminoglycosides (*aph(3'')-Ib, aph(6)-Id,* and *ant(3'')-Ia*), ampicillin (OXA-1 and TEM-95/-93), chloramphenicol (*catA1*), trimethoprim (*dfrA7, dfrA14* and *dfrA15*), sulfonamides (*sul1* and *sul2*), and tetracycline (*tet(A)* and *tet(D)*). Most AMR genes were associated with IncHI1 plasmids. However, the two MDR *S.* Typhi genotypes were associated with distinct plasmid lineages. The 3.1.1 MDR *S.* Typhi from Ghana (68 isolates) carried IncHI1 MDR plasmids of plasmid sequence type (PST) 2a, whilst the 4.3.1 MDR *S.* Typhi from Kenya (50 isolates) and Uganda (7 isolates), respectively carried ST6 and ST6a IncHI1 MDR plasmids. Minor differences in the specific AMR genes were also evident between these plasmid types (Figure 4.7). For example, the class I integron cassette contained *dfrA15* in the West African/PST 2a plasmid and *dfrA7* in East African/PST 6/6a plasmids, the latter plasmids also contained *sul2* and *tet(D)* which were absent from the West African isolates. Some outliers included, non-MDR *S.* Typhi isolates from Burkina Faso (genotype 2.2) with an IncX1 plasmid containing no resistance genes and Ghana (genotype 3.1.1) with an IncN plasmid displaying resistance against aminoglycosides (*aph(6)-Id*), ampicillin (TEM-95/-93), trimethoprim (*dfrA14*), and sulfonamides (*sul2*) and 5 non-MDR *S.* Typhi isolates (genotype 4.3.1) from Tanzania with IncFIB plasmids carrying the *aph(3'')-Ib, aph(6)-Id*), TEM-95/-93, *dfrA14,* and *sul2* resistant genes and an MDR *S.* Typhi isolate (genotype 4.3.1) from Kenya with an IncHI1 and IncQ1 plasmid associated with resistance genes against aminoglycosides (*aph(3'')-Ib, aph(6)-Id*), ampicillin (TEM-95/-93), chloramphenicol (*catA1*), trimethoprim (*dfrA7*), sulfonamide (*sul1* and *sul2*), and tetracycline (*tet(A)* and

tet(D)) (Figure 4.7). Additionally, none of the four MDR organisms from Tanzania possessed a detectable plasmid backbone. Using Bandage to investigate the location of MDR cassettes, I found that these isolates carried multiple AMR genes (*aph(3'')-Ib*, *aph(6)-Id*), TEM-95/-93, *catA1*, *dfrA7*, *sul1*, *sul2)* on a 24-kb composite chromosomal transposon (Tn2670-like element) inserted between coding sequences STY3618 and STY3619 (Wong *et al.* 2015).

In total, 16% (39/249) of the contemporaneous African *S.* Typhi exhibited reduced susceptibility against ciprofloxacin (9 from Kenya and 30 from Uganda). The Kenyan organisms exhibited the common mutation associated with reduced susceptibility to fluoroquinolones in *S.* Typhi, a substitution from serine to phenylalanine at codon 83 (Ser83Phe) in *gyrA.* The Ugandan organisms harboured an alternative serine to tyrosine *gyrA* mutation also at codon 83 (Ser83Tyr) (Table 4.2).

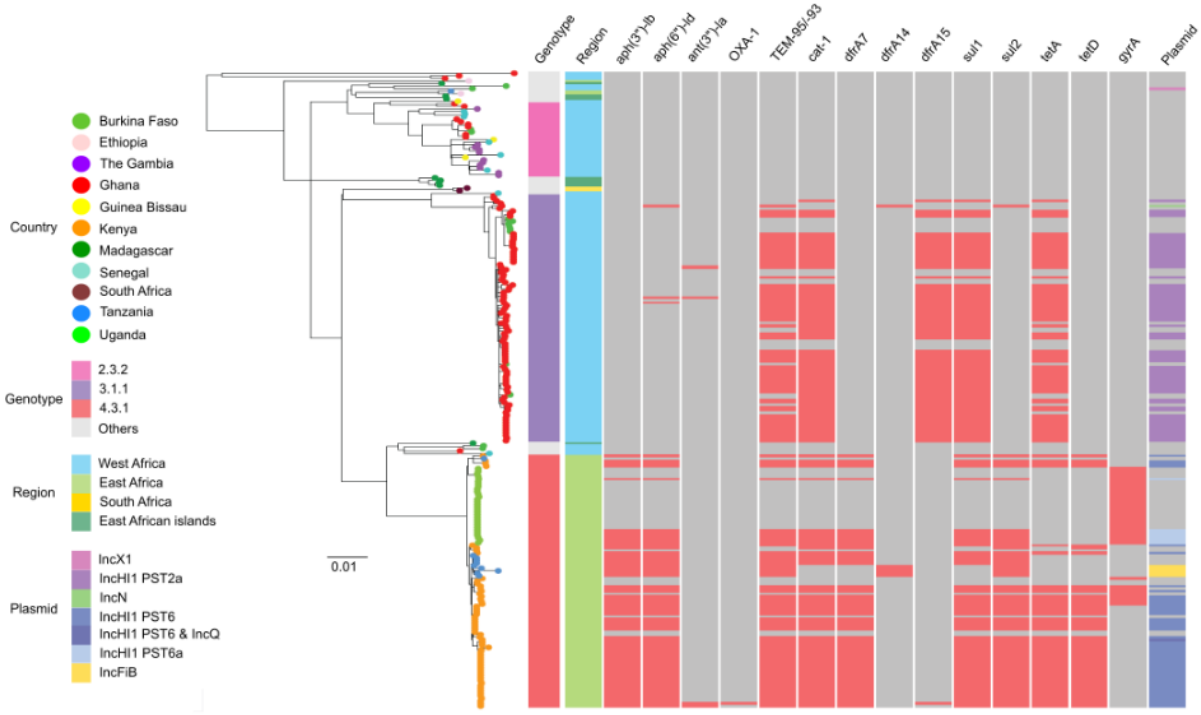


Figure 4.7 The antimicrobial resistance gene distribution within sub-Saharan African *S.* Typhi

Original legend (Park *et al.* 2018): "Maximum likelihood phylogenetic tree of 249 *S.* Typhi isolates from this study with corresponding metadata including genotype, location, antimicrobial resistance genes (AMR), and plasmids (see keys). Countries where *S.* Typhi isolates were isolated are highlighted by coloured circles at the tip of the branches. The three major genotypes and sub-regions of within the Africa continent are shown by the coloured bars; present AMR genes are shown in red. The scale bar indicates the number of substitutions per variable site."

4.3.4 The incidence of MDR typhoid fever in sub-Saharan Africa

I next calculated the incidence of MDR typhoid fever in specific age groups in countries where MDR *S.* Typhi was isolated: Ghana, Kenya, and Tanzania (Table 4.3). The incidence of MDR *S.* Typhi exceeded 100/100,000-person years of observation (PYO) in specific age groups in Ghana (<15 years: 414/100,000 PYO; 95% confidence interval [CI], 333-515) and Kenya (<15 years: 398/100,000 PYO; 95% CI, 291-545), in all age groups in Kenya (263/100,000 PYO; 95% CI, 199-347) and in the urban site in Tanzania (103/100,000 PYO; 95% CI, 61-173). While Burkina Faso had a high overall incidence of typhoid (Marks *et al.* 2017), no MDR *S.* Typhi were detected; 2/14 isolates were resistant to chloramphenicol and co-trimoxazole. The highest incidence of MDR *S.* Typhi in a specific age group in a single location was in children aged 2-4 years in Ghana (747/100,000 PYO; 95% CI, 491-1135), followed by 5-14 year olds in Kenya (507/100,000 PYO; 95% CI, 352-729). In Kenya and Ghana, the only TSAP sites where *S.* Typhi were isolated from infants (aged 0-1 years), the incidences of MDR *S.* Typhi in this age group were 148 (95% CI, 48-458) and 60 (95% CI, 17-210) per 100,000 PYO, respectively. Generally, the incidence of MDR *S.* Typhi was substantially higher in children <15 years than in adults. An exception was in Tanzania, where MDR *S.* Typhi occurred in higher incidences in those aged ≥15 years than in young children (Table 4.3).

Table 4.3 The incidence of MDR *S.* Typhi in sub-Saharan Africa

Country[1]	Age group in years	PYO estimation[2]				Recruitment proportion[3]	Genome-sequenced *S.* Typhi cases[4]	Crude MDR *S.* Typhi cases	Crude MDR *S.* Typhi incidence per 100,000 PYO	Adjusted MDR *S.* Typhi cases	Adjusted MDR *S.* Typhi incidence per 100,000 PYO (95% CI)[5]
		Proportion of catchment population visiting study facility in case of fever (95% CI)	Catchment population	Catchment population adjusted by health-seeking behaviour	PYO						
Ghana[6]											
AAN	0-1	16% (14-18)	11222	1760	4080	41%	1	1	25	2	60 (17-210)
	2-4	16% (13-18)	8086	1268	2940	41%	17	12	306	22	747 (491-1135)
	0-4	n.a.	n.a.	n.a.	n.a.	n.a.	18	13	n.a.	n.a.	n.a.
	5-14	16% (15-17)	34439	5415	12554	623/1657 (38%)	23	16	96	24	252 (177-357)
	<15	n.a.	53747	8443	19574	n.a.	41	29	97	81	414 (333-515)
	≥15	n.a.	n.a.	n.a.	n.a.	n.a.	22	16	n.a.	n.a.	n.a.
	Non_TSAP[6]	n.a.	n.a.	n.a.	n.a.	n.a.	38	23	n.a.	n.a.	n.a.
	All	n.a.	n.a.	n.a.	n.a	n.a.	101	68	n.a.	n.a.	n.a.
Kenya											
Kibera	0-1	42% (38-47)	3467	1456	2031	99/99 (100%)	5	3	148	3	148 (48-458)
	2-4	39% (36-43)	3070	1197	2039	312/312 (100%)	11	7	343	7	343 (164-720)
	5-14	43% (39-47)	7514	3231	5722	539/539 (100%)	32	29	507	29	507 (352-729)
	<15	n.a.	14051	5884	9792	n.a.	48	39	398	39	398 (291-545)
	≥15	35% (32-38)	15263	5342	9228	301/301 (100%)	11	11	119	11	119 (66-215)
	All	n.a.	29314	11227	19020	n.a.	59	50	263	50	263 (199-347)
Tanzania[7]											
MR[8]	0-1	4% (0-11)	24289	390	693	79%	0	0	0	0	0
	2-4	2% (0-4)	25281	406	721	79%	0	0	0	0	0
	5-14	13% (10-16)	118219	15487	27508	79%	1 (2) *	0	0	0	0
	<15	n.a.	167789	16283	28922	n.a.	1 (2) *	0	0	0	0
	≥15	2% (1-2)	298948	5172	9186	79%	2 (4) *	0	0	0	0
	All	n.a.	466737	21454	38108	n.a.	3 (6) *	0	0	0	0
MU[9]	0-1	7% (0-19)	10406	335	595	79%	0	0	0	0	0
	2-4	2% (0-6)	10831	348	618	79%	0	0	0	0	0
	5-14	13% (8-19)	37309	4850	8615	79%	3 (9) *	2 (7) *	12 (81) *	1 (9) *	15 (3-84) (103 (54-199)) *
	<15	n.a.	58546	5533	9828	n.a.	3 (9) *	2 (7) *	10 (71) *	1 (9) *	10 (1-72) (91 (47-175)) *
	≥15	n.a.	125746	2138	3796	79%	4 (8) *	2 (4) *	53 (105) *	3 (5) *	67 (19-229) (133 (56-319)) *
	All	n.a.	184292	7671	13626	n.a.	7 (17) *	4 (11) *	29 (81) *	4 (14) *	29 (11-78) (103 (61-173)) *

Original legends (Park *et al.* 2018):

[1] The TSAP study has data from total 10 countries, of which 9 countries (Burkina Faso, Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, and Tanzania in alphabetical order) found blood culture confirmed *S.* Typhi isolates circulating in the respective sites. These *S.* Typhi isolates have been whole genome sequenced for detection of multidrug resistant (MDR) genes. In addition, *S.* Typhi isolates yielded from 2 other surveillance activities in Uganda and The Gambia have been added to this analysis. Of these 11 countries, *S.* Typhi isolates with MDR genes were detected in Ghana from West Africa and Kenya, Tanzania, and Uganda from East Africa. Incidence of MDR *S.* Typhi in Uganda could not be estimated due to insufficient data on age stratification of patients, catchment population, healthcare seeking behaviour and recruitment proportion, which were applied uniformly for the analysis presented in this table for Ghana, Kenya, and Tanzania.

[2, 3] PYO estimation and recruitment proportion have been published in detail in the TSAP typhoid burden paper.

[4] Genome sequenced *S.* Typhi case numbers in this table may not exactly match the crude *S.* Typhi case numbers reported in the TSAP typhoid burden paper due to few sequencing failures.

[5] Adjusted incidence rates per 100,000 PYO (95% CI): adjustments for case recruitment and error factors.

[6] Ghana samples include non-TSAP projects as outlined in Chapter 9 (appendices).

[7,*] Tanzania: Enrolment algorithm has been applied to the crude MDR *S.* Typhi case numbers, i.e. recruitment by every 5th patient if enrolled before Nov 11th 2011 and every 2nd patient if enrolled after then. 1 isolate from Tanzania, which was from outside the study catchment area (“Moshi Other”) is not included in this incidence table due to the insufficient background data required as mentioned in this footnote.

[8] MR: Moshi Rural

[9] MU: Moshi Urban

4.4 Discussion

Here, I presented a contemporary dataset of *S.* Typhi genome sequences and AMR data from across sub-Saharan Africa generated through a major population-based surveillance study with data augmented from further locations. I exploited these data to assess the circulation of MDR *S.* Typhi genotypes and to calculate the incidence of MDR typhoid infections across the continent. My results have major implications for the use of empirical antimicrobials for treating febrile disease of presumed bacterial origin and future interventions for controlling typhoid in Africa.

Despite the broad genetic diversity observed within the continental *S.* Typhi population, I identified only three principal *S.* Typhi genotypes. These genotypes were geographically limited East (genotype 4.3.1) and West (genotypes 3.1.1 and 2.3.2) Africa. MDR *S.* Typhi in Africa is currently dominated by genotypes 4.3.1 and 3.1.1. *S.* Typhi 4.3.1 has been previously reported to circulate only in East Africa on the African continent (Wong *et al.* 2015; Feasey *et al.* 2015; Kariuki *et al.* 2010), with 3.1.1 dominating in Nigeria and circulating amongst neighbouring countries in West Africa (Wong *et al.* 2016b). After the likely importation from South Asia within the last 20 years, the extant population of *S.* Typhi 4.3.1 in Kenya, Tanzania, and Uganda has been formed through multiple introductions from South Asia followed by local expansions. Conversely, *S.* Typhi 3.1.1, which were isolated in Ghana, Burkina Faso, and Nigeria, do not appear to have recent ancestral roots in Asia, but have undergone localised microevolution within West Africa in recent decades. I speculate that these organisms have been transferred, maintained, and selected through the sustained movement of people and antimicrobial usage in West Africa. The MDR 4.3.1 *S.* Typhi from Kenya and Uganda also commonly exhibited mutations in *gyrA*, associated with reduced

susceptibility to fluoroquinolones, which has also been reported in Africa in recent years. Conversely, no *gyrA* mutations were found in the MDR *S.* Typhi 3.1.1 from Ghana. These data mirror recent reports from Nigeria (Wong *et al.* 2016b), and suggest that first-line antimicrobial agents (ampicillin, chloramphenicol, and co-trimoxazole) for the treatment of febrile diseases are still in common use in West Africa.

The acquisition of an MDR phenotype in *S.* Typhi is typically associated with IncHI1 plasmids, which have long been considered the main vehicle for resistance to first-line antimicrobials in *S.* Typhi (Holt *et al.* 2011). The distinct MDR lineages of *S.* Typhi found in West and East Africa, each associated with a distinct IncHI1 plasmid sequence type, suggest that *S.* Typhi and its AMR plasmids have not been transferred laterally across the continent. This may be because genotype 4.3.1 MDR *S.* Typhi has been circulating for a sufficient period in Africa to reach the West African region. Furthermore, the four MDR *S.* Typhi isolates from Tanzania did not harbour plasmid-associated sequences, suggesting that these AMR genes are inserted into the chromosome, as has been observed previously in Asia (Wong *et al.* 2015; Chiou *et al.* 2015; Ashton *et al.* 2015) and Zambia (Hendriksen *et al.* 2015). The integration of AMR genes into the *S.* Typhi chromosome is a worrying development, as it provides a mechanism for stable vertical transmission of the MDR phenotype without the potential fitness deficit associated with maintaining large plasmids, increasing the likelihood that MDR will be sustained during the ongoing spread of related *S.* Typhi across East Africa.

Here, I identified specific populations that are most at risk of MDR typhoid, which particularly warrants a reconsideration of current empirical antimicrobial use for treatment of typhoid. Generally, I found that the site incidences of MDR *S.* Typhi

corresponded largely with the overall burden of typhoid in the various study sites (Marks *et al.* 2017) (i.e. countries with high incidences of typhoid also had high incidences of MDR *S.* Typhi). Consequently, Kenya and Ghana exhibited the highest incidences of MDR typhoid in the sampled countries. Notably, Burkina Faso, which had a high burden of typhoid, had no incidence of MDR *S.* Typhi in comparison to neighbouring Ghana. Further, I found that children aged <15 years, the highest at-risk age group for typhoid in Africa, also generally exhibited the highest incidence rates of MDR *S.* Typhi infections. This age distribution of typhoid caused by MDR *S.* Typhi was not consistent across the continent, as those aged >15 years in Tanzania exhibited a higher incidence of MDR *S.* Typhi than younger children. Alternatively, some sites with a high burden of typhoid in specific age groups had no MDR infections. I suggest that this distribution is likely to mirror access to, and the generic usage of, specific antimicrobial agents in these locations and age groups, warranting the need for continued country/site-specific surveillance, review of local treatment policies, and the collection of antimicrobial usage data.

The incidence of MDR typhoid varied dramatically between settings and also between age groups in some individual locations. This discrepancy may be due to differing exposures to antimicrobials in different settings and age groups, which could lead to differential selective pressures in local circulating bacterial populations. My data additionally indicate that AMR/MDR *S.* Typhi are not only spread through local population movements in East and West Africa but can also arise *de novo*. This phenomenon can be observed within the microevolution and expansion of 3.1.1 MDR *S.* Typhi in West Africa. The AMR genes associated with 4.3.1 MDR *S.* Typhi in East Africa appear to be both plasmid and chromosomally located. This observation, coupled

with the acquisition of reduced susceptibility to fluoroquinolones, transmission between East African countries, and the importation of organisms from South Asia, raises further concerns regarding the progression of AMR in *S.* Typhi in Africa. 4.3.1 *S.* Typhi has spread successfully cross South Asia and become increasingly resistant to ciprofloxacin, making treatment options more limited (Thanh *et al.* 2016). The pervasiveness of AMR in 4.3.1 *S.* Typhi in South Asia has been recently highlighted by an outbreak of a ceftriaxone-resistant 4.3.1 *S.* Typhi in Hyderabad, Pakistan, which appears to be resistant to commonly available antimicrobial classes (Klemm *et al.* 2018). I predict that new AMR phenotypes that emerge in 4.3.1 *S.* Typhi in Asia are periodically introduced into East Africa. Further, the emergence of MDR *S.* Typhi 4.3.1 in South Africa suggests possible spread from East Africa to Southern Africa through human population movement, however this notion requires further investigation (Keddy *et al.* 2016).

This study highlights locations in sub-Saharan Africa where MDR typhoid is prevalent and where future activities to control its spread from Asia into Africa and also within Africa could be focused. In addition to continuing disease surveillance and investigating the genomic characteristics and phenotypic profiles of MDR *S.* Typhi, compiling antimicrobial usage data that can be linked with the distribution of AMR/MDR bacterial pathogens across Africa is becoming essential. The World Health Organization (WHO) prequalified a typhoid conjugate vaccine (TCV) in January 2018 with a recommendation to introduce the vaccine for infants and children older than six months in typhoid endemic countries (Burki 2018). Targeted vaccination programs at sites with a high burden of AMR/MDR *S.* Typhi could also be considered and may be informed by the age-stratified MDR disease incidence data presented here. New and potentially

highly efficacious *S.* Typhi conjugate vaccines are currently undergoing clinical trials and should become routinely available at the end of this decade (Burki 2018). Until these vaccines become available, countries in Africa with endemic typhoid should structure antimicrobial stewardship policies to control MDR *S*. Typhi and develop national roadmaps for their deployment.

Chapter 5 The phylogeography and incidence of multi-drug resistant iNTS disease in sub-Saharan Africa

All work described in Chapter 5 was presented at the 11th international conference on typhoid and other invasive salmonellosis, and posted on the Coalition Against Typhoid Website during my DPhil (Coalition against Typhoid (CaT) 11th international conference on typhoid and other invasive salmonellosis: Agenda – Take on Typhoid 2019).

5.1 Abstract

iNTS is one of the leading causes of bloodstream infections in sub-Saharan Africa. The disease burden is further exacerbated due to the emergence of MDR in various iNTS serovars. A total 166 iNTS isolates from eight African countries were whole genome sequenced, and the sequence data was subjected to a range of bioinformatics and phylogenetic analyses to investigate the multilocus sequence types, AMR genes, and plasmids. Major iNTS serovars were mapped onto a global phylogenetic framework to identify the likelihood of common ancestors and transmissions. *S.* Typhimurium ST313 (60%, 99/166) was the most predominant cause of iNTS disease in this sampling in Africa, followed by *S.* Enteritidis ST11 (17%, 28/166) and *S.* Dublin ST10 (11%, 18/166). *S.* Typhimurium ST313 and *S.* Enteritidis ST11 appeared to be pervasive in both West and South-eastern Africa while *S.* Dublin ST10 was found exclusively in West Africa. MDR was predominantly found in *S.* Typhimurium ST313 (95%, 95/99) and *S.* Enteritidis ST11 (25%, 7/28). Mutations in the *gyrA* gene associated with reduced susceptibility to fluoroquinolones were identified in *S.* Enteritidis and *S.*

Typhimurium in Ghana and an ST313 carrying a $bla_{\text{CTX-M-15}}$ was identified in Kenya. The pSLT virulence-resistance plasmid was consistently found in *S.* Typhimurium ST313; whereas a novel IncI1virulence-resistance plasmid (pSEP) was found in MDR *S.* Enteritidis ST11. Overall, the incidence of MDR iNTS disease exceeded 100/100,000-person years of observation (PYO), especially in children aged <15 years in the West African countries of Burkina Faso, Ghana, and Guinea-Bissau. I found evidence of inter-country transmission of *S.* Typhimurium ST313 lineage II between Ghana and neighbouring countries (Mali, Burkina Faso, and Nigeria), while multiple lineages of *S.* Enteritidis ST11 were identified with evidence of endemic circulation in Madagascar, South Africa, Ghana (Global epidemic clade) and inter-country transmission between West African countries (West Africa clade and Global epidemic clade). I identified a significant burden of MDR iNTS disease in the sampled locations in sub-Saharan Africa. Various MDR iNTS serovars and STs are being maintained in Africa. Routine surveillance, better antimicrobial stewardship and development of multivalent iNTS vaccine are urgently needed.

5.2 Introduction

Previous studies have shown that the majority of iNTS infections in human populations in sub-Saharan Africa are associated with *S.* Typhimurium and *S.* Enteritidis, both are associated with an MDR phenotype (Okoro *et al.* 2012); Leekitcharoenphon *et al.* 2013; Feasey *et al.* 2014; Kariuki *et al.* 2015a). ST313 is the most common genotype of *S.* Typhimurium and has been found in many African countries. The population structure of ST313 isolates in Africa is currently comprised of two distinct lineages (I and II), of which lineage I may originate from Malawi (only limited data available) and then spread to neighbouring countries from 1960. Lineage II was likely to have emerged

around 1977 from the Democratic Republic of Congo (DRC) and subsequently spread to Western Africa to replace lineage I (Okoro *et al.* 2012). *S.* Enteritidis is typically associated with human gastroenteritis and was increasingly reported during the late 1970s and 1980s in the Americas, Europe and parts of Africa (Senegal, Tunisia) due to the increased consumption of eggs and poultry (Rodrigue, Tauxe and Rowe 1990). Several outbreaks of foodborne illness caused by *S.* Enteritidis have been reported in African countries (Muvhali *et al.* 2017). *S.* Enteritidis is generally considered to cause self-limiting enterocolitis and largely susceptible to antimicrobials in comparison to other serovars; however, systemic bloodstream infections caused by MDR *S.* Enteritidis has been on the rise in Africa (Rodríguez *et al.* 2012). *S.* Enteritidis has been estimated to account for 33% of the total human iNTS disease burden in Africa (Ao *et al.* 2015). A genomic epidemiological investigation of a global collection of *S.* Enteritidis originating from 45 countries and 6 continents from 1948 to 2013 identified three clades associated with independent epidemics. These were a global epidemic clade that was largely susceptible to antimicrobials and caused both human enterocolitis and invasive disease and two MDR clades that emerged in Africa (the West African and Central/Eastern African clades) and are predominantly associated with bloodstream infections (Feasey *et al.* 2016).

In addition to *S.* Typhimurium and *S.* Enteritidis, a number of other NTS *Salmonella* serovars have also been identified as important causes of invasive disease in different settings in Africa. These include *S.* Isangi in South Africa (Feasey *et al.* 2010), *S.* Concord in Ethiopia (Beyene *et al.* 2011), and *S.* Stanleyville and *S.* Dublin in Mali (Tennant *et al.* 2010). Therefore, the epidemiology of iNTS disease in Africa is highly complex as *Salmonella* serovars tend to have different propensity to develop resistance

to antimicrobials and may have distinct epidemiological characteristics, which creates a major challenge for the control and prevention of the disease (Crump *et al.* 2015). A better understanding of host susceptibility, the mode of transmission of different NTS serovars and closely monitoring their trend in prevalence and development of AMR are crucial to implement proper measures to limit the spread of these pathogens in human populations.

Here, I aimed to investigate the distribution of iNTS serovars/STs, AMR determinants and estimate the incidence of MDR iNTS disease across sub-Saharan Africa. In addition, I also conducted a comprehensive phylogeographical analyses by mapping *S.* Typhimurium ST313 lineage II and *S.* Enteritidis ST11 organisms isolated from my study to the existing global population frameworks of *S.* Typhimurium ST313 and *S.* Enteritidis.

5.3 Results

5.3.1 The distribution of iNTS genotypes and serovars in sampled African countries

Among 166 iNTS isolates yielded from 8/10 African countries where TSAP surveillance was conducted, *S.* Typhimurium (ST313 and ST19), *S.* Enteritidis (ST11), and *S.* Dublin (ST10) were the most predominant iNTS serovars-STs circulating in sub-Saharan Africa. Specifically, 66% (110/166) of the isolates were *S.* Typhimurium, of which ST313 was dominant (90%, 99/110), followed by ST19 (10%, 11/110); *S.* Enteritidis accounted for 18% (30/166) of the isolates comprising of ST11 (93.3%, 28/30), ST183 (3.3%, 1/30) and ST2107 (3.3%, 1/30) and *S.* Dublin (ST10) ranked third and accounted for 11% (18/166) of all iNTS isolates. Other minor serovars-STs

isolated included *S.* Muenster ST321 (1/166), *S.* Poona ST308 (1/166), *S.* Stanleyville ST339 (1/166), *S.* Virchow ST359 (1/166), and *S.* Choleraesuis ST145 (3/166) (Table 5.1).

In West African countries, the majority of iNTS were *S.* Typhimurium ST313 and *S.* Enteritidis ST11; Burkina Faso (ST313=50%, 6/12; ST11= 33.3%, 4/12), Ghana (ST313=68%, 90/133; ST11=14%, 18/133), Guinea-Bissau (ST313=22%, 2/9; ST11=11%, 1/9) and Senegal (ST11=50%, 1/2). Notably, *S.* Dublin ST10 was isolated in Burkina Faso (8%, 1/12) and Ghana (13%, 17/133) in West Africa. In South-eastern Africa, *S.* Enteritidis ST11 and *S.* Typhimurium-ST19 were commonly detected; Tanzania (ST19=75%, 3/4), South Africa (ST11=100%, 1/1), Madagascar (ST11=75%, 3/4; ST19=25%, 1/4), while ST313 was only found in Kenya (100%, 1/1). *S.* Typhimurium ST19 was found in several West African countries with differing prevalence between countries; Burkina Faso (8%, 1/12); Ghana (2%, 2/133), Guinea-Bissau (33%, 5/9), and Senegal (50%, 1/2).

Overall, 61% (102/166) of the iNTS isolates were MDR. MDR iNTS isolates were distributed across the sampled African countries including Burkina Faso (83%, 10/12), Ghana (66%, 88/133), Guinea-Bissau (22%, 2/9), Kenya (100%, 1/1), and Senegal (50%, 1/2). *S.* Typhimurium exhibited highest prevalence of MDR (85%, 94/110) of which 95% (94/99) of ST313 isolates were MDR, whereas none of the ST19 isolates (0/11) were MDR; 23% (7/30) of *S.* Enteritidis and 6% (1/18) *S.* Dublin were MDR (Figure 5.1, Table 5.2).

Table 5.1 The distribution of iNTS serovars and genotypes circulating in the sampled countries in sub-Saharan Africa

Country (no. of iNTS[1]) (a)	Serovars	No. of iNTS per serovar (b)	% of total no. of iNTS per country (b)/(a)	Genotype (Sequence type)	No. of iNTS per genotype (c)	% of total no. of iNTS per country (c)/(a)
Burkina Faso (12)	Typhimurium	7	58%	313	6	50%
				19	1	8%
	Enteritidis	4	33%	11	4	33%
	Dublin	1	8%	10	1	8%
Ghana (133)	Typhimurium	92	69%	313	90	68%
				19	2	2%
	Enteritidis	20	15%	11	18	14%
				183	1	1%
				2107	1	1%
	Dublin	17	13%	10	17	13%
	Muenster	1	1%	321	1	1%
	Poona	1	1%	308	1	1%
	Stanleyville	1	1%	339	1	1%
	Virchow	1	1%	359	1	1%
Guinea Bissau (9)	Typhimurium	5	56%	313	2	22%
				19	3	33%
	Enteritidis	1	11%	11	1	11%
	Choleraesuis	3	33%	145	3	33%
Kenya (1)	Typhimurium	1	100%	313	1	100%
Madagascar (4)	Typhimurium	1	25%	19	1	25%
	Enteritidis	3	75%	11	3	75%
Senegal (2)	Typhimurium	1	50%	19	1	50%
	Enteritidis	1	50%	11	1	50%
South Africa (1)	Enteritidis	1	100%	11	1	100%
Tanzania (4)	Typhimurium	3	75%	19	3	75%
	Unknown	1	25%	2533	1	25%

Total 8 Countries[2] (166 iNTS isolates)(d)	Serovars	No. of iNTS per serovar (e)	% of total no. of iNTS in all 8 countries (e)/(d)	Genotype (Sequence type)	No. of iNTS per genotype (f)	% of total no. of iNTS in all 8 countries (f)/(d)
	Typhimurium	110	66%	ST313	99	60%
				ST19	11	7%
	Enteritidis	30	18%	ST11	28	17%
				other STs[3]	2	1%
	Dublin	18	11%	ST10	18	11%
	Others	8	5%	Other STs[4]	8	5%

[1] iNTS: invasive nontyphoidal *Salmonella*

[2] Total 8 countries: Burkina Faso, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, and Tanzania presented in this table. No iNTS isolates were yielded in Sudan and Ethiopia.

[3] Other sequence types of *S.* Enteritidis detected: 1 ST183 (isolate yielded from Ghana; age/sex unknown due to missing data) and 1 ST2107 (from Ghana; a 22 year old female); both non-MDR and no antimicrobial resistant genes detected.

[4] Sequence types of the other NTS serovars: 1 Muenster ST321 (yielded from Ghana; age/sex/year unknown due to missing data), 1 Poona ST308 (yielded from Ghana in 2008; age/sex unknown due to missing data), 1 Stanleyville ST339 (yielded from Ghana; age/sex/year unknown due to missing data), 1 Virchow ST359 (from Ghana; age/sex/year unknown due to missing data), 3 Choleraesui ST145 (2 isolates yielded from 1 year old female infants in 2010 and 2011 and 1 from 3 year old female infant in 2012; all from Guinea-Bissau), 1 Unknown ST2533 from Tanzania.

Table 5.2 The distribution of MDR iNTS and *gyrA* mutation (fluoroquinolone resistance) in the sampled countries in sub-Saharan Africa

Serovars (number of isolates) N=166	**MDR iNTS isolates per serovars**	**MDR iNTS serovar per country (%, number)**	**MDR iNTS per genotype (%, number)**
Typhimurium (n=110)	85% (94/110)	Burkina Faso (50%, 6/12) Ghana (64%, 85/133) Guinea Bissau (22%, 2/9) Kenya (100%, 1/1)	ST313 (95%,94/99) ST19 (0%, 0/11)
Enteritidis (n=30)	23% (7/30)	Burkina Faso (33%, 4/12) Ghana (2%, 2/133) Senegal (50%, 1/2)	ST11 (25%, 7/28)
Dublin (n=18)	6% (1/18)	Ghana (1%, 1/133)	ST10 (6%, 1/18)
Others (n=8)	0% (0/8)	n.a.	n.a.

Countries (no. of iNTS)	**No. of MDR iNTS (N=102)**	**% of MDR iNTS**	***gyrA***
Burkina Faso (n=12)	10	10/12 (83%)	0
Ghana (n=133)	88	88/133 (66%)	S83Y (ST313, 2 isolates) D87G (ST11, 6 isolates) D87Y (ST11, 2 isolates) D87N (ST11, 3 isolates)
Guinea-Bissau (n=9)	2	2/9 (22%)	0
Kenya (n=1)	1	1/1 (100%)	0
Senegal (n=2)	1	1/2 (50%)	0

[1] Multidrug resistance (MDR) definition used for the analysis presence of resistant genes for at least one agent in all three antimicrobial categories listed below (detected in this study): Ampicillin (blaCTX_M, blaOXA, blaTEM), Chloramphenicol: (*catA1*), Trimethoprim-sulfamethoxazole (sulfonamide (sul1, sul2) and trimethoprim (*dfrA, dfrA1, dfrA14, dfrA8*)).

[2] Refer to Table 1 for the number of iNTS isolates per country used as a denominator to calculate the % of MDR per country in this table.

[3] The 2 MDR iNTS isolates with *gyrA* mutation (fluoroquinolone resistance) were yielded from a 1 year old female infant and 10 month old female infant in Agogo in 2011 (TSAP: Typhoid Fever Surveillance Program).

[4] *Spv* locus were detected in all MDR iNTS isolates.

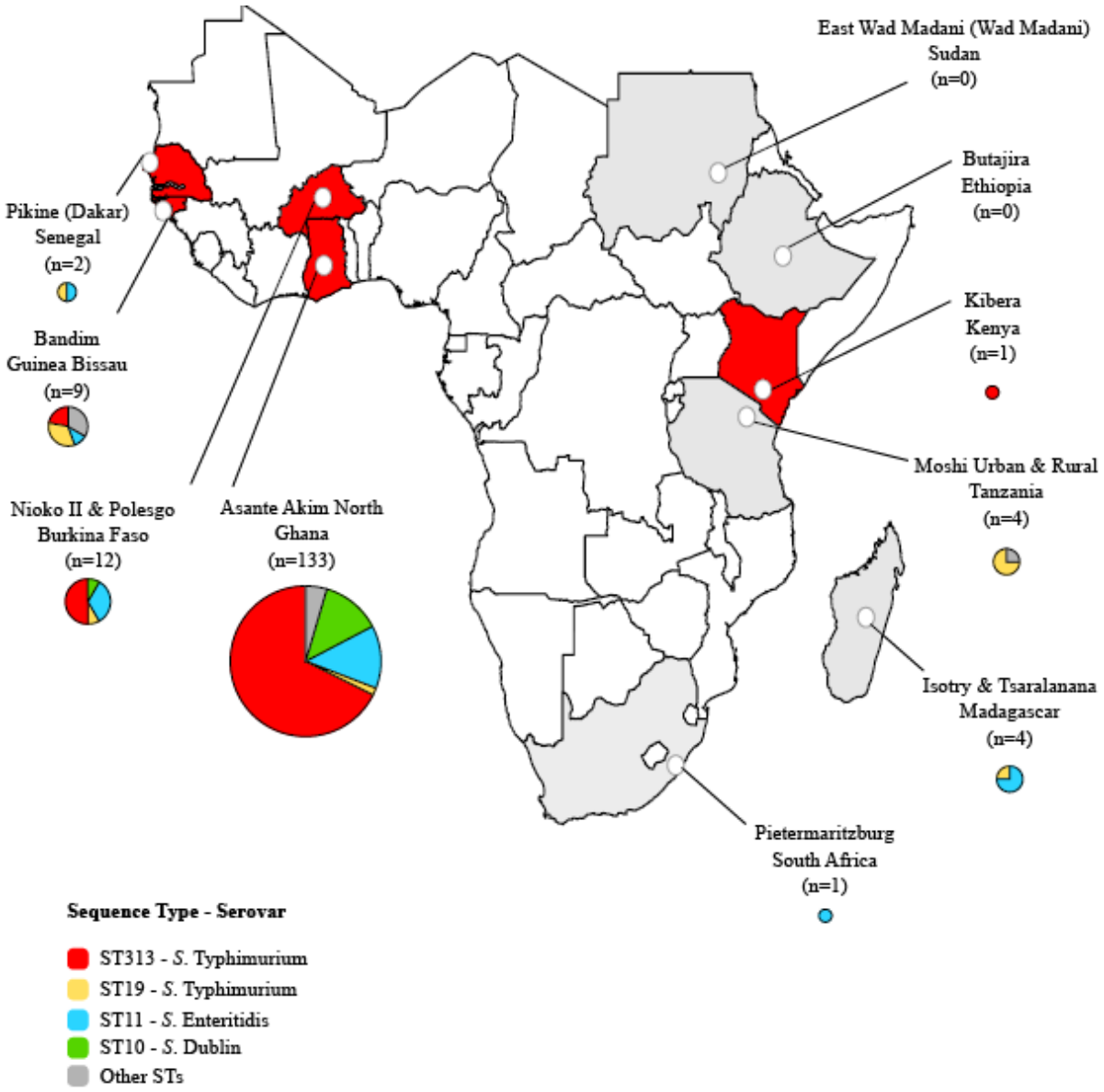


Figure 5.1 The geographical distribution of iNTS genotypes and serovars in the sampled countries in sub-Saharan Africa

Different colours in the pie charts correspond to different sequence types and serovars of iNTS isolates in my study sites. The size of the pie charts corresponds to the numbers of isolates in each country. Countries highlighted in red and grey are with and without MDR iNTS isolates respectively.

5.3.2 The phylogenetic structure and MDR determinants of iNTS serovars

Predictably, the three major iNTS serovars (*S*. Typhimurium ST313/ST19, *S*. Enteritidis ST11, and *S*. Dublin ST10) formed four distinct clusters, and exhibited a dissimilar AMR gene content (Figure 5.2). Almost all the MDR *S.* Typhimurium ST313 isolates (95%; 94/99) carried the Tn21 transposon-associated MDR loci (*sulII-strAB-dfrA1-aad A1-sulI-cat-blaTEM*) on an IncF virulent plasmid pSLT as reported previously (Okoro *et al.* 2012). One MDR *S.* Typhimurium ST313 isolate from Kenya additionally carried two copies of $bla_{\text{CTX-M-15}}$, conferring resistance to third generation cephalosporins, one of which was found on the 300kb IncHI2 plasmid, pKST313 (accession number: LN794248). The other copy of $bla_{\text{CTX-M-15}}$was inserted into the chromosome and disrupted the *ompD* locus. 5/99 *S.* Typhimurium ST313 isolates harboured the pSLT plasmid, but were not MDR due to the absence of the plasmid-borne MDR locus. Quinolone resistance was uncommon in *S.* Typhimurium ST313; only 2/99 Ghanaian ST313 isolates harboured the S87Y mutation in the *gyrA* gene (Table 5.2).

In comparison to *S.* Typhimurium ST313, the *S.* Enteritidis ST11 isolates were largely non-MDR (21/28; 75%) (Table 5.2). However, two Ghanaian isolates had acquired an AMR cassette (*sul2-strAB-tetA)* associated with a small (11kb) non-conjugative IncQ plasmid. This IncQ plasmid exhibited a similar genetic structure to the plasmid pSTU288-2 from *S.* Typhimurium (accession number CP004059.1, coverage 98%, identity 99%). Additionally, two other Ghanaian isolates carried a Tn21-mediated AMR cassette (*sulII-strAB-dfrA1-aadA1-sulI-cat)* on the virulence plasmid, and one isolate from Madagascar carried a *bla*TEM-bearing Tn3 transposon inserted into the virulence plasmid. The majority of *S.* Enteritidis ST11 isolates (19/28; 68%) harboured a typical IncF virulence plasmid of about 60kb, similar to the pSENV plasmid (accession number

NC_019120.1, coverage 100%, identity 99%). The remaining isolates (9/28; 32%) harboured a novel IncI1 virulence-resistance plasmid (pSEP) of approximately 68kb (Figure 5.3); 7 isolates (4/Burkina Faso, 2/Ghana, 1/Senegal) carried the MDR Tn21-like transposon (*sulII-strAB-tetB-dfrA1-sulI-cat-blaTEM*), and 2 isolates carried an AMR cassette (*TnpA-sulII-strAB-blaTEM-Tn3*), conferring resistance to ampicillin, streptomycin, and sulphanomides. This IncI1 plasmid exhibited 60% homology to the pSENV virulence plasmid, and did not harbour the IncF replicons, the fimbriae-encoding operon (*pefBACDI*), or the adjacent virulent-associated genes *srgA* and *rck* (Figure 5.3). Quinolone resistance was predicted in 39% (11/28) of *S.* Enteritidis-ST11 isolates, all of which originated from Ghana, displaying differing resistant mutations in *gyrA* (D87G: 6 isolates, D87N: 3 isolates, and D87Y: 2 isolates) (Table 5.2).

The majority of *S.* Dublin ST10 isolates (17/18; 94%) were pan- susceptible to antimicrobials, except for one Ghanaian isolate that carried an MDR Tn21 transposon-mediated cassette (*sulII-strAB-dfrA1-aadA1-sulI-cat-blaTEM*) (Figure 5.2). All *S.* Dublin ST10 isolates carried a typical IncF virulence plasmid (75kb), which was similar to plasmid pOU1115 (accession number: NC_010422.1, coverage 100%, identity 99%).

None of the *S.* Dublin ST10 isolates possessed mutations in *gyrA* (Table 5.2) and the viaB operon, encoding the Vi polysaccharide, was absent from all *S.* Dublin isolates. Further, all isolates clustering within the *S.* Typhimurium ST19 lineages, as well as other uncommon serovars-genotypes, had not acquired any AMR and were pan-susceptible. The majority of iNTS isolates (97%, 161/166) carried the virulence plasmid containing the spv locus. The exceptions were five iNTS isolates belonging to the uncommon serovars of iNTS disease (1 Muenster, 1 Poona, 1 Stanleyville, 1 Virchow, 1

unidentified serovar) did not harbour the virulence plasmid.

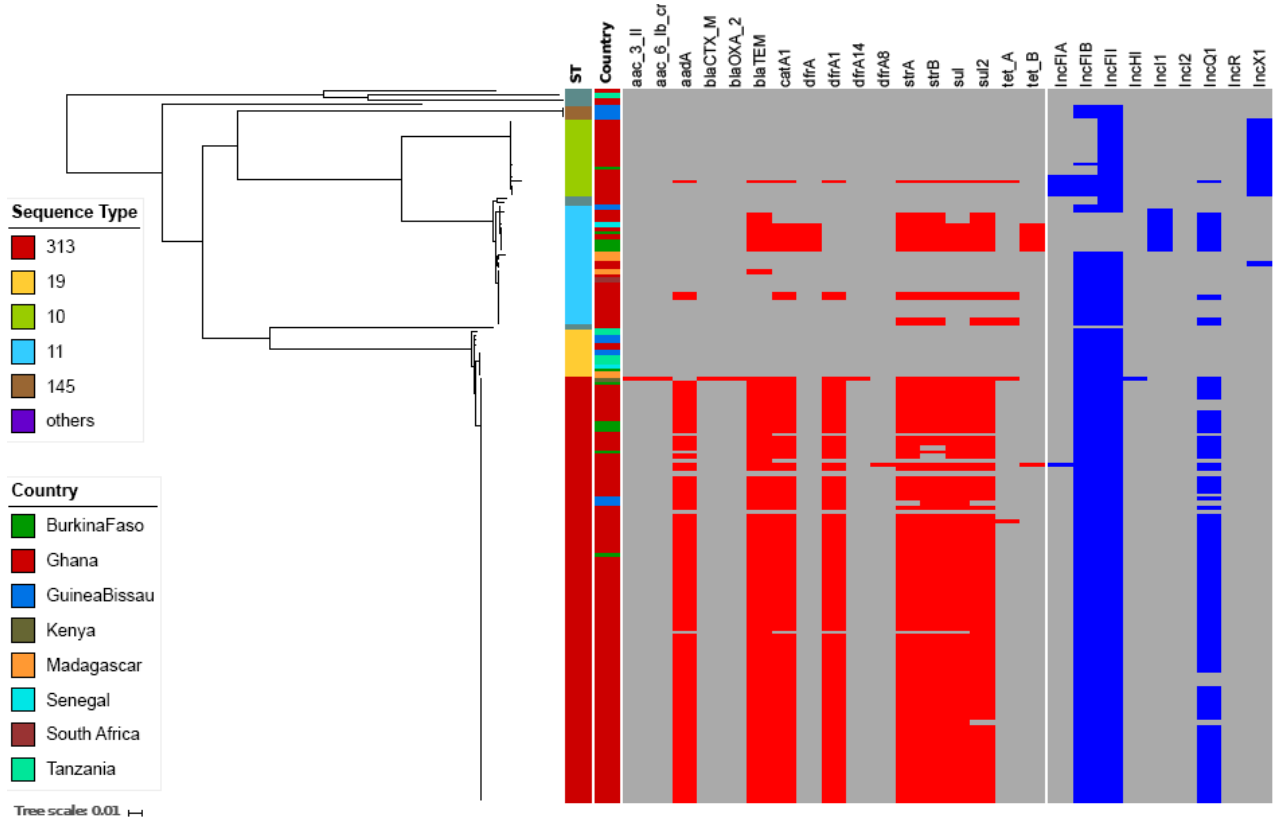


Figure 5.2 Antimicrobial resistant genes and plasmids associated with iNTS isolates circulating in sampled sub-Saharan Africa countries

Maximum likelihood phylogenetic tree based on the core genes of all my iNTS isolates and their corresponding metadata. First column shows the sequence types in different colour. Second column corresponds to the countries where my iNTS isolates were detected. The remaining columns exhibit a heatmap of detected AMR genes and plasmid replicons. The tree scale bar indicates the number of substitutions per variable site.

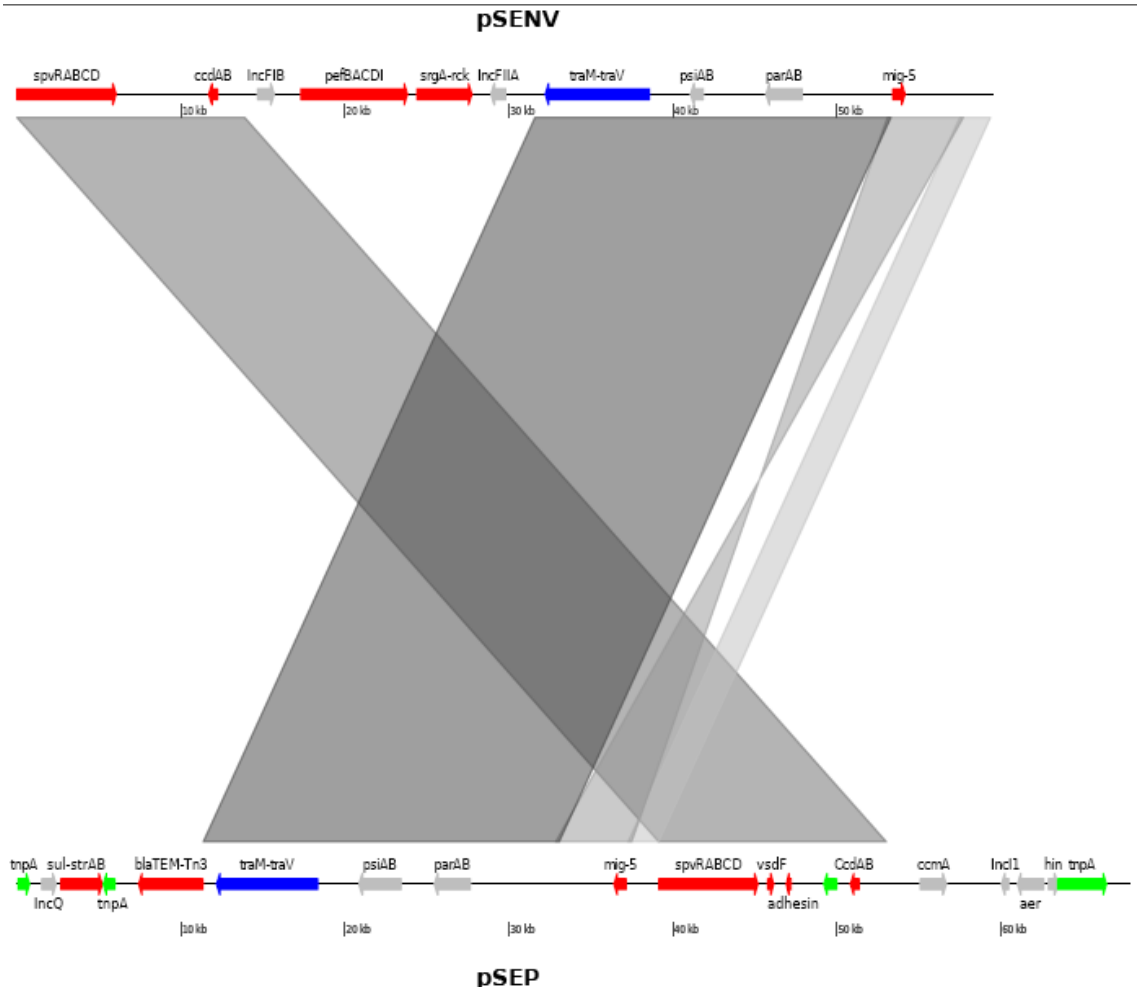


Figure 5.3 Novel IncI1 virulence-resistance plasmid (pSEP) in an *S.* Enteritidis ST11 isolate

Plasmid comparison analyses between the novel virulence-resistance IncI1 plasmid pSEP (bottom) and the reference virulence IncF plasmid pSENV (top). The grey blocks show the BLASTn comparison between the two plasmids. Some annotations are added for both plasmids. Red coloured arrows are genes associated with virulence and AMR. Blue coloured arrows are genes associated with conjugation. Grey coloured arrows correspond to plasmid replication and stability. Green coloured genes are associated with transposon elements.

5.3.3 The phylogeography of *S.* Typhimurium ST313 lineage II and *S.* Enteritidis ST11

All *S.* Typhimurium ST313 isolates from this study fell into the lineage II, which suggested that the lineage I may no longer be circulating in these countries. A Kenyan *S.* Typhimurium ST313 isolate that carried two copies of $bla_{\text{CTX-M-15}}$ gene was part of the previously described clonal expansion of ceftriaxone-resistant ST313 subclade in Kenya (Kariuki *et al.* 2015a). The ST313 isolates from Ghana did not form a single cluster but were well distributed around the phylogenetic tree and displayed a high degree of genetic diversity. This suggests these organisms may have been circulating in Ghana for some time. The ST313 isolates from Ghana clustered tightly with isolates from Mali, Burkina Faso, and Nigeria on several occasions, indicating regular movement of organisms between Ghana and these neighbouring countries in West Africa. (Figure 5.4a)

Regarding the *S.* Enteritidis ST11 isolates, 11/28 (40%) (Ghana: 5, Burkina Faso: 4, Senegal: 1, Guinea Bissau: 1) were in a West African clade that was associated with AMR and invasive human infections (Feasey *et al.* 2016). In this study, the *S.* Enteritidis ST11 isolates belonging to this West African clade displayed a high predicted level of AMR (7 MDR isolates, 2 isolates resistant to ampicillin, streptomycin and sulphonamides). Additionally, 4 isolates clustered within an Outlier cluster, of which 2 Ghanaian isolates clustered with isolates from the U.S. and 2 isolates from Madagascar clustered with isolate from Mauritius; all these organisms were pan-susceptible to antimicrobial. Notably, 13/28 (46%) isolates (Ghana 11, Madagascar: 1, South Africa: 1) belonged to the Global epidemic clade, which has been shown to cause

both enterocolitis in Western countries and invasive salmonellosis in African countries. Within this clade, the isolates from Madagascar and South Africa were part of the endemic clones circulating in these countries; whereas the Ghanaian isolates not only formed a separate cluster but also clustered with isolates from the neighbouring countries, such as Cameroon and Senegal (Figure 5.4b).

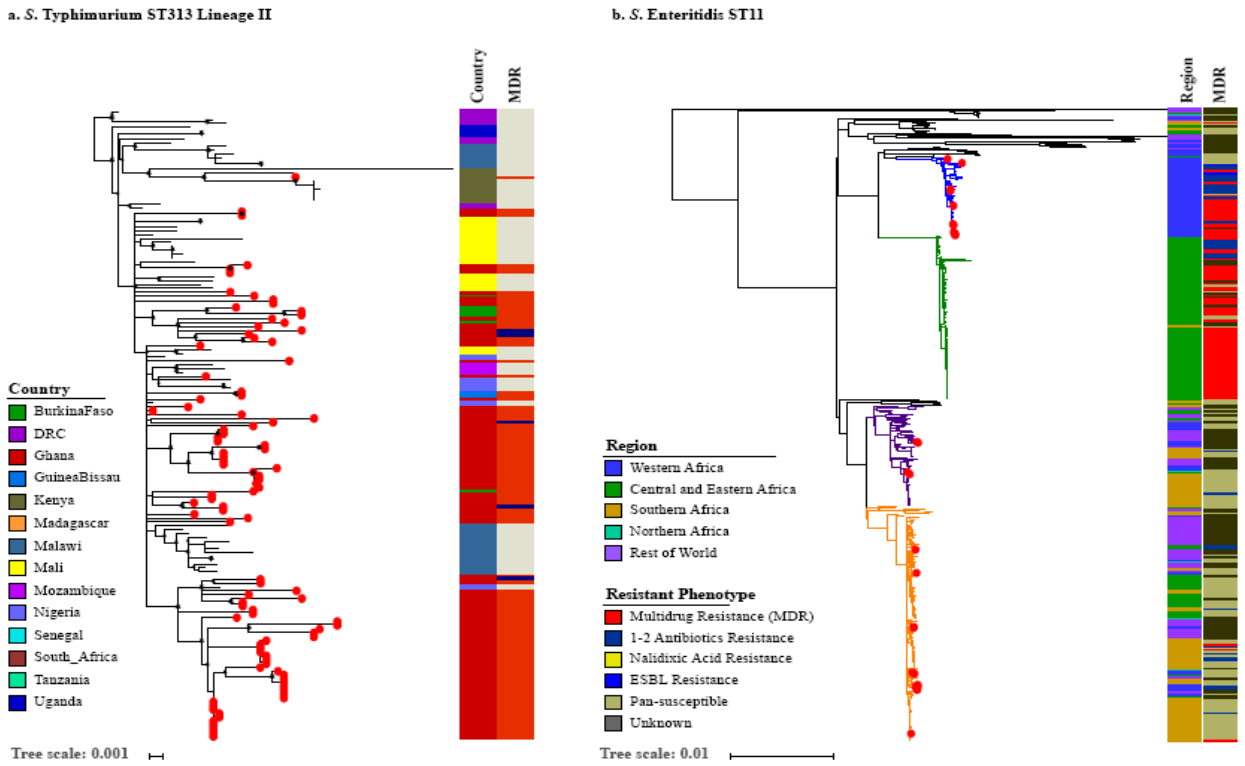


Figure 5.4 The phylogeography of *S.* Typhimurium ST313 lineage II and *S.* Enteritidis ST11 in sub-Saharan Africa

a) Maximum likelihood phylogenetic tree of my *S.* Typhimurium-ST313 lineage II isolates in the context of sub-Saharan Africa continent. Red circles at the terminal leaves correspond to my study isolates. First column shows different colour-coded countries from where all analysed isolates originate. Second column shows MDR, non-MDR, and xxx isolates in red, grey, and blue respectively. **b)** Maximum likelihood phylogenetic tree of my *S.* Enteritidis-ST11 isolates in the global context of *S.* Enteritidis. Red circles at the terminal leaves correspond to my study isolates. First and second columns show regions and resistant phenotypes in different colours. The tree scales indicate the number of substitutions per variable site.

5.3.4 The incidence of MDR iNTS disease in sub-Saharan Africa

I next estimated the age stratified incidences of MDR iNTS disease in four African countries (Burkina Faso, Ghana, Guinea-Bissau, and Kenya) (Table 5.3). The incidence of MDR iNTS disease in Senegal could not be estimated due to unavailable data, but a case of MDR iNTS was detected in an infant aged seventeen months. Overall, the incidence of MDR iNTS disease exceeded 100/100,000-person years of observation (PYO) in children <15 years of age in all Western African countries: Burkina Faso (NiokoII, 274/100,000 PYO, 95% confidence interval [CI], 185-406; and Polesgo, 255/100,000 PYO, 95% CI, 138-470), Ghana (Asante Akim North: Ghana-AAN, 414/100,000, 95% CI, 333-515), and Guinea-Bissau (Bandim, 105/100,000, 95% CI, 69-161). Among this specific age group (<15 years), younger children (<2-4 years) exhibited the highest MDR iNTS incidences in both sites in Burkina Faso: 753/100,000 PYO (95% CI, 460-1233) in NiokoII and 630/100,000 PYO (95% CI, 288-1380) in Polesgo. In Ghana-AAN, infants aged <1 year experienced the highest incidence of MDR iNTS disease (1435/100,000; 95% CI, 1110-1854) followed by children aged between 2 and 5 years (747/100,000; 95% CI, 491-1135). The incidence rate of MDR iNTS in older age groups (≥15 years) remained low, ranging between 0 (Guinea-Bissau), to 11 (Kenya), and 54 (Burkina Faso) per 100,000 PYO.

Table 5.3 The incidence of MDR iNTS disease in sub-Saharan Africa

Country[1]	Age group in years	PYO estimation[2]				Recruitment proportion[3]	Genome-sequenced iNTS cases	Crude MDR iNTS cases	Crude MDR iNTS incidence per 100,000 PYO	Adjusted MDR iNTS cases	Adjusted MDR iNTS incidence per 100,000 PYO (95% CI)[4]
		Proportion of catchment population visiting study facility in case of fever (95% CI)	Catchment population	Catchment population adjusted by health-seeking behaviour	PYO						
Burkina Faso											
Nioko II	0-1	81% (74-88)	2208	1788	2097	247/1297 (19%)	2	1	48	5	251 (107-590)
	2-4	81% (75-86)	1823	1477	2097	235/1259 (19%)	3	3	143	16	753 (460-1233)
	5-14	81% (78-84)	4295	3479	4889	228/889 (26%)	2	1	20	4	79 (29-214)
	<15	n.a.	8326	6744	9083	n.a.	7	5	55	25	274 (185-406)
	≥15	81% (79-83)	9428	7637	10676	208/759 (27%)	1	1	9	4	35 (13-96)
	All	n.a.	17754	14381	19759	n.a.	8	6	30	29	145 (100-209)
Polesgo	0-1	92% (86-99)	896	824	929	117/475 (25%)	1	1	108	4	431 (162-1147)
	2-4	83% (76-89)	856	710	992	148/466 (32%)	2	2	202	6	630 (288-1380)
	5-14	87% (83-91)	1734	1509	2104	252/510 (49%)	0	0	0	0	0
	<15	n.a.	3486	3043	4025	n.a.	3	3	75	10	255 (138-470)
	≥15	87% (84-89)	4088	3557	4917	239/629 (38%)	1	1	20	3	54 (16-179)
	All	n.a.	7574	6600	8942	n.a.	4	4	45	13	144 (83-249)
Ghana[5]											
AAN	0-1	16% (14-18)	11222	1760	4080	41%	88	24	588	59	1435 (1110-1854)
	2-4	16% (13-18)	8086	1268	2940	41%	23	9	306	22	747 (491-1135)
	0-4	n.a.	n.a.	n.a.	n.a.	n.a.	111	33	n.a.	n.a.	n.a.
	5-14	16% (15-17)	34439	5415	12554	623/1657 (38%)	6	6	48	16	126 (77-206)
	<15	n.a.	53747	8443	19574	n.a.	117	39	147	81	414 (333-515)
	≥15	n.a.	n.a.	n.a.	n.a.	n.a.	16	10	n.a.	n.a.	n.a.
	All_TSAP	n.a.	n.a.	n.a.	n.a.	n.a.	133	49	n.a.	n.a.	n.a.
	Non_TSAP[6]	n.a.	n.a.	n.a.	n.a.	n.a.	49	39	n.a.	n.a.	n.a.
	All	n.a.	n.a.	n.a.	n.a	n.a.	182	88	n.a.	n.a.	n.a.
Guinea Bissau											
Bandim	0-1	46% (39-54)	10852	4992	5198	206/631 (33%)	7	2	96	15	291 (176-482)
	2-4	43% (37-48)	7307	3142	3866	175/359 (49%)	1	0	26	2	53 (13-208)
	5-14	42% (41-48)	19905	8360	11101	187/380 (49%)	1	0	18	4	37 (14-97)
	<15	n.a.	38064	16494	20165	n.a.	9	2	40	21	105 (69-161)
	≥15	45% (43-47)	62694	28212	37109	105/163 (64%)	0	0	0	0	0
	All	n.a.	100758	44706	57274	n.a.	9	2	14	21	37 (24-57)
Kenya											

Kibera	0-1	42% (38-47)	3467	1456	2031	99/99 (100%)	0	0	0	0	0
	2-4	39% (36-43)	3070	1197	2039	312/312 (100%)	0	0	0	0	0
	5-14	43% (39-47)	7514	3231	5722	539/539 (100%)	0	0	0	0	0
	<15	n.a.	14051	5884	9792	n.a.	0	0	0	0	0
	≥15	35% (32-38)	15263	5342	9228	301/301 (100%)	1	1	11	1	11 (2-77)
	All	n.a.	29314	11227	19020	n.a.	1	1	5	1	5 (1-37)
Senegal[7]											
Pikine	0-1	39% (32-46)	20120	7837	11194	n.a.	0	0	n.a.	n.a.	n.a.
	2-4	37% (33-41)	30180	11097	15851	n.a.	1	1	n.a.	n.a.	n.a.
	5-14	31% (28-34)	96152	29807	42577	n.a.	0	0	n.a.	n.a.	n.a.
	<15	n.a.	146452	48741	69623	n.a.	1	1	n.a.	n.a.	n.a.
	≥15	30% (28-31)	195726	58718	83874	n.a.	1	0	n.a.	n.a.	n.a.
	All	n.a.	342178	107459	153496	n.a.	2	1	n.a.	n.a.	n.a.

[1] TSAP was performed in 10 countries, of which 8 countries (Burkina Faso, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, and Tanzania in alphabetical order) exhibited positive iNTS isolates confirmed via whole genome sequencing. MDR iNTS were found in 5/8 countries presented in this table. No MDR iNTS were detected via whole genome sequencing from the isolates yielded from Madagascar, South Africa, and Tanzania.

[2, 3] PYO estimation methodologies have been published in detail in the TSAP typhoid burden paper (Marks et al, Lancet Global Health, 2017).

[4] Adjusted MDR iNTS incidence per 100,000 PYO (95% CI): adjustments for case recruitment and error factors.

[5] Ghana samples included in this estimation of MDR iNTS are from the TSAP only.

[6] Non-TSAP includes other fever surveillance performed in Agogo ("IsolateAgogo", "FISA", and "TYSA"). Refer to the method section.

[7] Adjusted MDR incidence of iNTS per 100,000 PYO could not be estimated for the study site in Senegal due to unavailable data on the recruitment proportion. The one MDR iNTS patient confirmed and presented in this table (Crude MDR iNTS case) was a male infant aged 17 months, infected in 2012 with *S.* Enteritidis ST11. The one non-MDR iNTS patient presented in this table (Genome-sequenced iNTS case) were a male adult aged 66 years, infected in 2012 with *S.* Typhimurium.

5.4 Discussion

Since the late 1980s, invasive disease caused by NTS serovars has become a significant health problem in sub-Saharan Africa, particularly in infants and children. Despite the fact that the majority of iNTS disease has been caused by only two *Salmonella* serovars (Typhimurium and Enteritidis), various other serovars have also been documented to cause bloodstream infections with similar clinical symptoms (Feasey *et al.* 2010; Beyene *et al.* 2011; Tennant *et al.* 2010). NTS are generally associated with animal reservoirs and infection is typically via the consumption of contaminated food from animal origins (Morpeth, Ramadhani and Crump 2009); however, the sources and predominant mode of transmission of iNTS serovars in Africa are largely unknown and different serovars may have a distinct host range and transmission patterns. Moreover, typhoid has been increasingly reported in Africa, which further exacerbates the burden of invasive salmonellosis on this continent (Stanaway *et al.* 2019). Antimicrobial therapy is essential to treat patients with invasive *Salmonella* disease and to reduce mortality. However, the effectiveness of antimicrobial therapy is diminishing due to the emergence and dissemination of various MDR NTS serovars (Feasey *et al.* 2016; Kingsley *et al.* 2009). Previous NTS surveillance in humans, animals and the environment often lacked advanced molecular genotyping techniques that can provide further insights into the bacterial transmission and can be standardized across African countries (Baker *et al.* 2018). Routine surveillance with the integration of WGS represents a powerful approach to closely monitor the spread of AMR pathogens and to detect novel AMR clones that are epidemiologically and clinically important in a timely manner (Baker *et al.* 2018). In this chapter, I presented a comprehensive genomic epidemiological investigation of contemporaneous iNTS isolates from a standardized surveillance of bloodstream infection in multiple countries in sub-Saharan Africa. My

findings outlined the distribution of predominant MDR iNTS serovars and genotypes circulating across African countries, some of their potential international transmission dynamics, MDR determinants and an estimation of age-stratified incidence of MDR iNTS infections.

My data demonstrated that the majority of bloodstream infections in sub-Saharan Africa in sampled countries were caused by two predominant serovars-genotypes, *S.* Typhimurium ST313 and *S.* Enteritidis ST11; however, their distribution was variable between countries and regions. In West Africa, *S.* Typhimurium ST313 was dominant in Burkina Faso, Ghana, Guinea-Bissau but was not isolated in Senegal. Conversely, in South-eastern Africa, ST313 was exclusively detected in Kenya. *S.* Enteritidis ST11, though less common than ST313, appeared to be pervasive in both West (Burkina Faso, Ghana, Guinea-Bissau, Senegal) and South-eastern Africa (South Africa, Madagascar). Here, *S.* Dublin ST10 emerged as the third most common cause of bloodstream infection but was restricted to the West African countries of Burkina Faso and Ghana. In addition, *S.* Typhimurium ST19 was also associated with a number of invasive infections, as described before (Okoro *et al.* 2012) and was geographically dispersed across the continent, including West (Burkina Faso, Ghana, Guinea-Bissau, Senegal) and South-eastern Africa (Tanzania, Madagascar).

A small number of organisms belonging to uncommon serovars were also isolated from patients with bacteremia in Ghana (*S.* Virchow ST359, *S.* Poona ST308, *S.* Muenster ST321, and *S.* Stanleyville ST339) and Guinea-Bissau (*S.* Choleraesuis ST145). I found a high prevalence of MDR in the iNTS isolates, this MDR gene composition was mostly associated with *S.* Typhimurium ST313 and *S.* Enteritidis ST11 and one MDR *S.*

Dublin ST10 isolate. It is evident that MDR ST313 and ST11 are well distributed throughout West African countries (Burkina Faso, Ghana, Guinea-Bissau, and Senegal), while in South-eastern Africa, MDR ST313 was only found in Kenya. The MDR resistant gene cassettes were located on the IncF virulence plasmid in ST313 and a newly described IncI1 virulence plasmid in ST11, suggesting that the MDR phenotype is likely to be maintained in the bacterial population, with the possibility of further horizontal gene transfer. Particularly, MDR *S.* Enteritidis ST11 appears to be an emerging cause of bloodstream infections in West Africa and several African countries have reported an increasing trend of bacteremia caused by *S.* Enteritidis (Sow *et al.* 2007; Keddy *et al.* 2017). Additionally, I identified reduced susceptibility to fluoroquinolones in two ST313 isolates and eleven ST11 isolates from Ghana; one ceftriazone-resistant ST313 isolate from Kenya also carried two copies of $bla_{\text{CTX-M-15}}$ on the chromosome and on a plasmid, indicating that resistance to other important classes of antimicrobials is also increasing in Africa. Invasive *Salmonella* with reduced susceptibility to ciprofloxacin have been reported in Burkina Faso (Marks *et al.* 2017) and Ghana (Nielsen *et al.* 2012; Marks *et al.* 2017), Nigeria (Akinyemi, Bamiro and Coker 2007), Senegal (Harrois *et al.* 2014), Mozambique (Mandomando *et al.* 2009a), and the Congo (Lunguya *et al.* 2013). An outbreak of MDR ST313 carrying $bla_{\text{CTX-M-15}}$ has been reported in Kenya and Malawi (Feasey *et al.* 2014; Kariuki *et al.* 2015a). It is likely that the widespread use of ceftriazone and ciprofloxacin for the empirical treatment of febrile illnesses of presumed bacterial origins in Africa will eventually lead to a continued increase and spread of resistance bacteria on this continent, which is likely to amplify the issue of iNTS infection. As a result, routine surveillance and antimicrobial stewardship are required to provide revised guidelines for clinical management and public health interventions for iNTS infections.

In this chapter, I additionally reconstructed the phylogeography of the two predominant serovars-genotypes (*S.* Typhimurium ST313 and *S.* Enteritidis ST11) to investigate their potential movement across the continent. All *S.* Typhimurium ST313 isolates (95% MDR) from my dataset fell into a single lineage (lineage II) and there was some evidence of movement between Ghana and neighbouring countries (Burkina Faso, Guinea-Bissau, Senegal, Nigeria) in West Africa. In contrast, ST11 isolates belonged to three distinct lineages: the global epidemic clade, the West African clade and an Outlier cluster; all MDR ST11 isolates clustered within the West Africa clade. These MDR ST11 isolates have spread between the West African countries of Ghana, Burkina Faso and Senegal, and should be carefully monitored through strengthened and continued surveillance. In South-eastern Africa, ST11 isolates was found to circulate in Madagascar (Outlier cluster and global epidemic clade) and South Africa (global epidemic clade); however, none of these isolates were MDR. The fact that multiple lineages of ST11 are associated with bloodstream infections is worrying as various lineages of ST11 can be associated with multiple transmission pathways and may have the ability to acquire a wide range of virulence-resistance plasmids (Rodríguez *et al.* 2012).

I calculated a substantial burden of MDR iNTS disease (incidence rate >100/100,000 PYO) in the West African countries of Burkina Faso, Ghana (<5 years), and Guinea-Bissau (< 2 years). The incidence of MDR iNTS disease presented here generally corresponds to the incidence of iNTS disease (Marks *et al.* 2017) in respective countries. In Ghana-AAN, MDR *S.* Typhi were most frequently isolated from children aged 2-4 years (Park *et al.* 2018), while MDR iNTS disease was highest in infants 0-1 years,

which corresponds with the age-stratified incidence rates of *S.* Typhi and iNTS disease in this site (Marks *et al.* 2017). Notably, in Burkina Faso, while no MDR *S.* Typhi were isolated (Park *et al.* 2018), I identified high incidences of MDR iNTS disease in both NiokoII and Polesgo; both sites had a high incidence (>100/100,000 PYO) of typhoid fever and iNTS disease (Marks *et al.* 2017). In Kibera, the incidence of typhoid fever (Marks *et al.* 2017) and MDR *S.* Typhi (Park *et al.* 2018) were higher than that of iNTS disease (Marks F. et al., 2017) and MDR iNTS disease. No MDR iNTS were detected in Moshi-Urban and Moshi-Rural sites in Tanzania where MDR *S.* Typhi incidences were reported in children aged 5-14 years and ≥15 years (Park *et al.* 2018). Same adjustment factors were used to estimate the incidences of MDR iNTS disease in this chapter and MDR typhoid fever in the previous chapter; healthcare seeking behaviour (proportion of the study catchment population seeking healthcare at the sentinel healthcare facilities in case of fever) and the proportion of eligible patients (meeting study inclusion criteria) not recruited or dropped out as described in the methodology chapter. Here, the presentation of fever was the criteria considered for these adjustments, not taking into account the prior usage of antibiotics nor other clinical presentations reported with iNTS disease such as fever with respiratory symptoms, gastrointestinal symptoms or both of these (MacLennan *et al.* 2017). This could be interpreted as an under-estimation the true burden of MDR iNTS disease among the study populations.

The high prevalence of MDR iNTS disease in young children in these countries is likely to undermine the effectiveness of therapy, which may lead to prolonged illness and increased risks to case fatalities though there is paucity of data on whether MDR increases mortality. A study on iNTS disease in hospital admitted Malawian children

exhibited high prevalence of MDR iNTS disease, and identified significant risk factors for case mortality, which included a history of dyspnea, absence of fever, presence of respiratory distress or hypoglycaemia at presentation, and HIV infection (MacLennan *et al.* 2017). The phenomenon of MDR iNTS may be a particular issue in areas with high burdens of malnutrition and malaria (Kariuki *et al.* 2015a). The development of safe and effective iNTS vaccines are warranted and should be introduced in malaria endemic settings with high burden of iNTS disease and malnutrition and particularly where MDR iNTS ST313 and ST11 predominate. Given the complex transmission mechanisms of iNTS/NTS serovars in comparison to *S.* Typhi, continued molecular surveillance of iNTS pathogens through one health approaches should be conducted in an attempt to control the NTS variants with the ability to cause human disease, as well as the host-adapted/generalized variants with zoonotic and/or human reservoirs.

In conclusion, *S.* Typhimurium (ST313 and ST19), *S.* Enteritidis (ST11), and *S.* Dublin (ST10) are the predominant NTS serovars associated with human invasive disease in the sampled locations in Africa. ST313, ST19, and ST11 appear to be pervasive across Africa, while ST10 is confined in West Africa. MDR was found largely in ST313 (both West and South-eastern Africa) and ST11 (West Africa), which was mediated by the IncF virulence plasmid pSLT and a novel IncI1 virulence plasmid pSEP, respectively. Regular transfer of MDR ST313 and MDR ST11 occurs between several West African countries. Closely monitoring the trends in the predominant serovars and AMR dynamics as well as antimicrobial stewardship and the development of polyvalent vaccine against iNTS serovars are urgently needed for the management and prevention of iNTS infections in Africa.

Chapter 6 A genetic characterisation of NTS associated with asymptomatic infection in Senegal and Guinea-Bissau

6.1 Abstract

Acute and chronic carriers of invasive and non-invasive salmonellosis serve a significant role in the transmission dynamics and endemicity of typhoid fever and iNTS/NTS disease through shedding of the organism. However, there is lack of data and knowledge on *Salmonella* shedding in symptomatic patients and asymptomatic individuals. Here, a subset of 2,436 people in the typhoid fever surveillance research catchment areas in Bissau, Guinea-Bissau and Dakar, Senegal were randomly selected (1,077 and 1,359 individuals respectively) to investigate the prevalence of *Salmonella* shedding. Stool specimens collected during 2012-2014 were cultured to isolate *Salmonella* organisms. Ultimately, 40 NTS organisms (26 and 14 in Bissau and Dakar, respectively) were isolated. WGS of these organisms revealed a diverse collection of NTS sequence types that were present in asymptomatic individuals residing in the surveyed communities. The majority of NTS organisms from human stool samples (69% (6/13) in Dakar and 96% (22/23) in Bissau) did not harbour any AMR genes. However, a small number of isolates exhibited resistance to some antimicrobials, including a *S.* Agona resistant to streptomycin, sulfonamides and tetracyclines, *S.* Chester and *S.* Hadar with resistant to streptomycin, co-trimoxazole and tetracyclines, and an ST3702 isolate carrying genes conferring resistant to trimethoprim and beta-lactams. Included in the collection was an *S.* Enteritidis ST11 isolated in Senegal carrying an IncF virulence plasmid with an spv locus, which is typically associated with invasive disease. Further molecular epidemiological research is warranted to better understand the complex

mechanisms of *Salmonella* shedding and transmission in context of pathogen survival and interaction with humans, animal hosts, and environmental reservoirs.

6.2 Introduction

The epidemiological characteristics of NTS infections have been well described in industrialized countries; the organisms are typically associated with a self-limiting gastroenteritis and via the consumption of contaminated food from an animal origin (Majowicz *et al.* 2010; Moore *et al.* 2011). However, in sub-Saharan Africa NTS organisms are a predominant cause of bacteraemia, while little is known about the source of infection and their transmission pathways. The presence of NTS organisms have been identified in food products, animals, the environment, children with diarrhoea, and asymptomatic infections in Africa, but the association of these organisms with invasive disease is uncertain as molecular typing of the organisms is not commonly performed (Obi *et al.* 1997; Sibhat *et al.* 2011; A. *et al.* 2013; Kotloff *et al.* 2013; Magwedere *et al.* 2015). Currently, the environmental reservoirs, host range and modes of transmission of iNTS in Africa remain poorly understood. The asymptomatic shedding of NTS appears to be common in healthy individuals in Africa (Obi *et al.* 1997; Kariuki *et al.* 2006; Sibhat *et al.* 2011; Kotloff *et al.* 2013; Im *et al.* 2016). An investigation into household and animal contacts of index cases of iNTS infection in Kenya reported that approximately 7% of human contacts had an apparent asymptomatic infection with an NTS organism; 66% of isolates were genetically indistinguishable from iNTS organisms in the corresponding index cases (Kariuki *et al.* 2006). Furthermore, the majority of NTS isolates from domestic animals in the household or environmental sources around the household was unrelated to iNTS organism, suggesting that the most likely mode of transmission was human-to-human

(Kariuki *et al.* 2002, 2006; Dione *et al.* 2011b)However, the prevalence of asymptomatic *Salmonella* infection in the human population and the extent to which they contribute to transmission, diarrheal disease, and invasive disease remains undetermined. Human-adapted *Salmonella* serovars such as Typhi and Paratyphi A are well known to establish a chronic carrier state, whereby the organisms are intermittently shed into the local environment, a mechanism that may aid in maintaining their transmission within the population (Gonzalez-Escobedo, Marshall and Gunn 2011). Similarly, there is evidence that iNTS serovars, such as *S.* Typhimurium ST313, have evolved to become better human-adapted in the immuno-compromised in Africa and may have the potential to develop a prolonged carriage (Okoro *et al.* 2014, 2015). There is a need for better molecular epidemiological investigations regarding the prevalence of asymptomatic NTS infections in the general population in Africa. Additionally, to understand the significance of asymptomatic infection we need to assess the phylogenetic relationship between iNTS from healthy individuals, whilst trying to assess the immune status of the host and whether we can define these individuals as "carriers". A previous report of household-level randomized stool culture survey of the general population in Dakar, Senegal and Bissau, Guinea-Bissau identified high prevalence of *Salmonella* excreters; however, this study lacked serotyping and genetic characterization of the *Salmonella* isolates. In this chapter, I conducted a genomic analysis of *Salmonella* isolates from asymptomatic individuals in Africa. By identifying the serovars/STs, AMR genes I aimed to investigate some insights into their potential links with invasive infection and diarrheal disease.

6.3 Results

6.3.1 The prevalence and distribution of NTS serovars and STs in the general

population of Senegal and Guinea-Bissau

Thirteen NTS isolates were isolated from 1,359 stool specimens taken from 1,869 individuals living in 211 households in Senegal. Overall, a wide variety of *Salmonella* serovars/STs were isolated in the stool cultures (9 serovars/STs from total 13 isolates); there was no difference in serovars/STs between age groups (Table 6.1). Out of the 13 NTS isolates, *S.* Corvallis ST1357 accounted for 23% (3/13) and was specifically isolated from three family members residing in the same household (including parents and a 2-year-old girl), suggesting intra-household transmission or a common source of infection. *S.* Chester ST1954 and *S.* Johannesburg ST515, each comprised of 15.4% (2/13) of the NTS isolates in Senegal. Other isolated serovars included *S.* Agona ST13 (1/13), *S.* Poona ST308 (1/13), *S.* Hadar ST33 (1/13), *S.* Enteritidis ST11 (1/13), *S.* Give ST516 (1/13) and ST3470/unidentified serovar (1/13).

Table 6.1 The distribution of NTS serovars and genotypes detected from human stool samples in Guinea-Bissau and Senegal

Site/Country (N=36)	Serovars	Genotype (ST [1])	Age (year)	Sex (F/M)	Residence [2]	Year
Bissau/ Guinea-Bissau (N=23)	NF [3]	3475	38	F		2012
	Durban	2126	5	F	H	2012
	Durban	2126	10	M	H	2012
	NF	3703	8	M	H	2012
	Give	516	21	M	H	2013
	Give	516	22	F	H	2013
	Give	516	32	M	H	2013
	NF	3468	28	F	H	2013
	Give	516	7	M	H	2013
	Give	516	31	F	H	2013
	NF	3468	0 (<1yr)	F	H	2013
	NF	3468	35	F	H	2013
	Give	516	30	F	H	2013
	NF	3468	6	F	H	2013
	NF	3702	6	F	H	2013
	NF	3702	12	M	H	2013
	NF	3702	15	M	H	2013
	Give	516	14	M		2012
	Virchow	755	0 (<1yr)	M		2012
	NF	3032	1	F		2012
	NF	3474	13	F		2012
	NF	3474	15	F		2012
	NF	NF	40	F		2012
Dakar/ Senegal (N=13)	Agona	13	3	F		2013
	Chester	1954	6	M		2013
	Chester	1954	17	M		2013
	Corvallis	1357	2	F	H	2013
	Corvallis	1357	19	F	H	2013
	Corvallis	1357	20	M	H	2013
	Enteritidis	11	29	F		2013
	Give	516	15	F		2013
	Hadar	33	7	M		2013
	Johannesburg	515	7	M		2013
	Johannesburg	515	18	F		2013
	Poona	308	59	F		2013
	NF	3470	48	F		2013

Genotype (ST) (n)	Serovars	Age (year)	Sex (F/M)	Country (N)
2126 (n=2)	Durban	5, 10	F, M	Guinea-Bissau
3032 (n=1)	NF	1	F	
3468 (n=4)	NF	0 (<1yr), 6, 28, 35	F, F, F, F	
3474 (n=2)	NF	13, 15	F, F	
3475 (n=1)	NF	38	F	
3702 (n=3)	NF	6, 12, 15	F, M, M	
3703 (n=1)	NF	8	M	
755 (n=1)	Virchow	0 (<1yr)	M	
NF (n=1)	NF	40	F	
11 (n=1)	Enteritidis	29	F	Senegal
13 (n=1)	Agona	3	F	
1357 (n=3)	Corvallis	2, 19, 20	F, F, M	
1954 (n=2)	Chester	6, 17	M, M	
308 (n=1)	Poona	59	F	
33 (n=1)	Hadar	7	M	
3470 (n=1)	NF	48	F	
515 (n=2)	Johannesburg	7, 18	M, F	
516 (n=8)	Give	7, 14, 21, 22, 30, 31, 32	M, M, M, F, F, F, M	Guinea-Bissau (n=7/23; 30%)
		15	F	Senegal (n=1/13; 8%)

[1] ST: Sequence type.
[2] Residency data was collected in GPS or address units (see Appendix 9.4), and the study participants with same GPS or address units are identified as those residing in the same household in this analysis. H: same household.
[3] NF: Not found.
[4] Guinea-Bissau: Total 23 NTS isolates.
[5] Senegal: Total 13 NTS isolates.

Similarly, there was a wide diversity of *Salmonella* STs isolated from 1,077 stool cultures from 1,299 individuals living in 164 households in Guinea-Bissau (Table 6.1). However, the majority of these STs are not commonly detected, and therefore the corresponding *Salmonella* serovars were unidentified. There was also no difference in the distribution of *Salmonella* serovars/STs between age groups in this setting (Table 6.1). The three most commonly detected serovars/STs in Guinea-Bissau were *S.* Give ST516 (30.4%, 7/23), ST3468/unidentified serovar (17.4%, 4/23), and ST3702/unidentified serovar (13%, 3/23). The remaining NTS isolates were *S.* Virchow ST755 (1/23), *S.* Durban ST2126 (2/23), ST3032 (1/23), ST3474 (2/23), ST3475 (1/23) and ST3703 (1/23). One isolate in Guinea-Bissau was untypeable by MLST. Notably, in this location I could identify the same *Salmonella* ST in the same household on more than one occasion; *S.* Durban ST2126 (one household: two children aged 5 and 10), *S.* Give ST516 (two households: one had three adults aged 21, 22 and 32 and one had a child aged 7 and a female aged 31), ST3468 (one household: a child aged below 1 year/NA and a female aged 35) and ST3702 (one household: three children aged 6, 12 and 15).

S. Give ST516 was the only serovar/ST isolated in both Senegal and Guinea-Bissau (Table 6.1). A minimum spanning tree reconstructed from the allelic profiles of all the NTS isolates demonstrated a high level of dissimilarity between these allelic profiles, by which almost all STs differed in at least 3 alleles from each other (Figure 6.1). The exception was one clonal complex comprised of a central genotype ST516 and ST3470 that shared five out of the seven MLST loci.

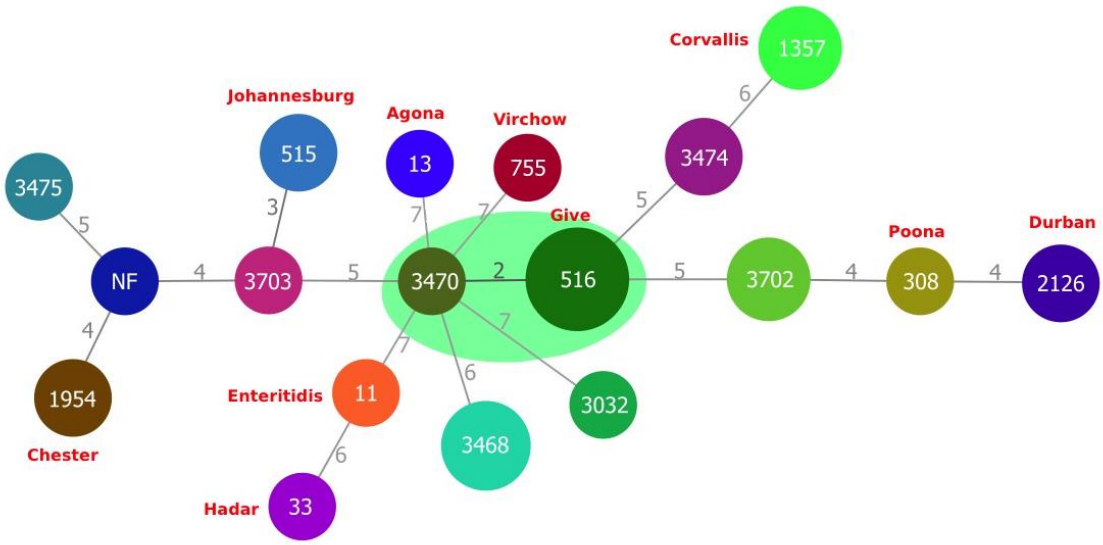


Figure 6.1 Minimum spanning tree of MLST data on 36 NTS isolates from stool culture survey in Guinea-Bissau and Senegal

Each circle represents a ST, which is proportional to the number of isolates. Green zone between ST516 and ST3470 indicates that these STs belong to the same clonal complex (CC). The various STs are colour-coded for reference, and the number on each of the branches corresponds to the number of allele different between each ST.

6.3.2 The phylogenetic relationship of a *Salmonella* Enteritidis ST11 isolate from an asymptomatic infection in a global context

Given the relevance of *S.* Enteritidis ST11 I aimed to investigate the organism isolated from an asymptomatic infection in more detail. I found that the *S.* Enteritidis ST11 from an asymptomatic stool sample in Senegal also carried a typical IncF virulence plasmid containing the spv locus that may enable the bacterial invasome and instigate a systemic illness (Guiney and Fierer 2011), similar to the pSENV plasmid (accession number NC_019120.1, coverage 100%, identity 99%). Therefore, I aimed to investigate the phylogenetic relationship between this isolate and all invasive *S.* Enteritidis ST11 from TSAP (28 isolates from Senegal, Ghana, Burkina Faso, South Africa, Madagascar, Guinea-Bissau and Ghana) and the global collection of 594 isolates from 48 countries.

A Maximum likelihood tree reconstruction showed that the *S.* Enteritidis ST11 from the asymptomatic stool sample in Senegal clustered in the Outlier Cluster in the global population structure of *S.* Enteritidis ST11 (Figure 6.2). This cluster was geographically and temporally diverse, containing isolates associated with both enterocolitis in Europe and bacteremia in South Africa and Malawi (Feasey *et al.* 2016). The isolate from the asymptomatic stool sample in Senegal was pan- susceptible to antimicrobials and did not harbour resistance associated mutations in the *gyrA* gene. Within the phylogenetic structure its nearest neighbour was a pan-susceptible isolate recovered from a stool specimen in Mauritania, a country neighbouring to Senegal. Conversely, the invasive isolate from Senegal (TSAP study) was MDR and fell into the West African Clade, a cluster primarily associated with MDR and human invasive disease. As the stool sample from Senegal was collected once and health status of individual was not accessed at the time of recruitment, it was impossible to determine the duration and its potential

contribution to transmission to diarrheal disease and/or invasive infections.

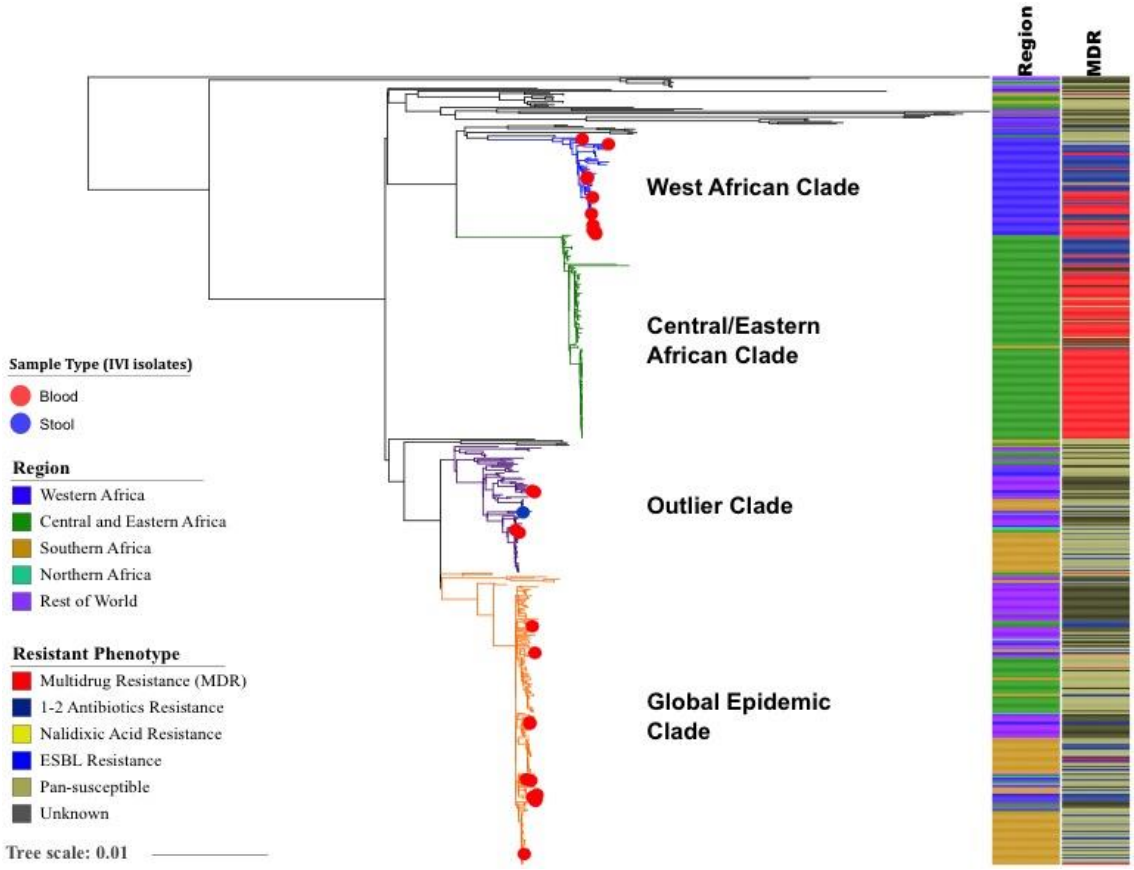


Figure 6.2 The phylogenetics of *S*. Enteritidis ST11 isolate from an asymptomatic stool sample in Senegal in a global context

Maximum likelihood tree showing the phylogenetic relationship between *S*. Enteritidis ST11 from stool sample in Senegal and all invasive ST11 strains from TSAP study in the context of global population structure. The four major clusters are highlighted in different colour, and the bars on the right correspond to regions and resistant phenotypes of the isolates. The stool isolate from Senegal is shown in blue circle, whereas blood isolates from TSAP study were highlighted in red circles at the terminal nodes.

6.3.3 The distribution of antimicrobial resistant genes and plasmids in NTS organisms isolated from asymptomatic stool samples in Senegal and Guinea-Bissau

Regarding the NTS organisms from asymptomatic stool samples in Senegal, 69% (9/13) of the isolates did not harbour any AMR genes. One *S.* Agona isolate (ST13) carried a collection of AMR genes on a chromosomally integrated class I integron (*Int*I1-*aadA7*-*qacE*-*sulI*-HP-transposase-*eamA*-*tetAR*), which conferred resistance against streptomycin, sulphonamides, and tetracyclines. Three isolates carried the quinolone resistance gene *qnrB19*, including two *S.* Chester ST1954 isolates and one *S.* Hadar ST33 isolate. Among these three isolates, one *S.* Chester ST1954 and one *S.* Hadar ST33 isolate additionally contained various genes encoding resistance against streptomycin, co-trimoxazole, and tetracyclines (*strAB*-*dfrA14*-*sulII*-*tetAR* and *strAB*-*dfrA14*-*sulII*-*tetAR*, respectively). I further inspected the sequences from these isolates using Bandage and found that these AMR gene cassettes were either integrated into the chromosome (*S.* Hadar ST33) or located on a small non-conjugative plasmid (*S.* Chester ST1954). Furthermore, I found that the *S.* Agona isolate harboured three mutations in quinolone resistance determining regions (QRDR), including two in the *gyrA* gene (S83F and D87N), and a single mutation in the *parC* gene (S80I). No QRDR mutations were found in the remaining isolates in Senegal. Three pan-susceptible NTS isolates, including two *S.* Johannesburg ST515 isolates and one ST3470 isolate from Senegal, carried a large IncFIB plasmid (>100 kb), which had an unknown function.

For the NTS isolated from asymptomatic individuals in Guinea-Bissau, the majority of isolates (96%, 22/23) did not contain any AMR genes, an exception was an ST3702 isolate carrying genes conferring resistant to trimethoprim (*dfrA14*) and beta-lactams

(*bla*$_{TEM}$). None of the NTS isolates in Guinea-Bissau had QRDR mutations . Four NTS isolates carried the same conjugative IncFII plasmid of about 80 kb (which shared a high level of genetic similarity to a plasmid in *S.* Bareilly, accession number: CP006054, coverage 80%), including *S.* Durban ST2126 (1), *S.* Give ST516 (2) and ST3702 (1).

6.4 Discussion

Since the early 1990s, iNTS has emerged as one of the leading causes of bloodstream infections in Africa. However, very little is known about its predominant modes of transmission, including disease reservoirs, transmission routes, the prevalence of healthy carriers and sub-clinical infections in the human population, the duration of asymptomatic carriage and shedding, the immune status of asymptomatic carriers or the risk factors for the development of asymptomatic shedding. The presence of iNTS organisms in animals, food products, and the environment has been rarely demonstrated in Africa; human-to-human transmission is hypothesised to be the most common mode of transmission (Kariuki *et al.* 2006). As a result, investigations on the prevalence of asymptomatic shedding and potential carriers of iNTS in the general population are required to better understand their role in disease transmission. For this purpose, the integration of genomics in conventional surveillances for iNTS carriage is useful tools for providing new insights into potential epidemiological links between organism circulation in the population and invasive disease.

In this study, I presented a detailed molecular characterization of NTS organisms isolated through a stool culture survey in the general populations of Dakar, Senegal and Bissau, Guinea-Bissau. I found a diverse range of *Salmonella* serovars/STs circulating in Senegal and Guinea-Bissau; with only one overlapping serovar/ST (*S.* Give ST516)

between these two countries. In Senegal, the majority of isolated *Salmonella* (*S.* Corvallis, Chester, Johannesburg, Agona, Poona, Hadar, and Enteritidis) have been commonly reported in previous surveillances of *Salmonella* from animal and animal products in African countries. For examples: *S.* Agona, *S.* Chester, *S.* Corvallis, *S.* Give, *S.* Hadar, *S.* Poona, *S.* Virchow were detected from poultry and pig in South Africa, (Gelaw, Nthaba and Matle 2018) and *S.* Corvallis was the third most common serovar found in various food, animals and environmental sources in Tunisia (Aissa *et al.* 2007). Sampling in the Gambia (Dione *et al.* 2011a), Senegal (Cardinale *et al.* 2003; Dione *et al.* 2011a), Burkina Faso (Kagambèga *et al.* 2013), Nigeria (Fashae *et al.* 2010), Ethiopia (Molla, Alemayehu and Salah 2011), Ghana (Andoh *et al.* 2016) identified a range NTS serovars from poultry (*S.* Agona, Enteritidis, Chester, Virchow, Poona, Corvallis, Give), sheep (*S.* Poona, Agona, Johannesburg), pigs (*S.* Give), and goats (*S.* Agona). In comparison, the distribution of *Salmonella* serovars/STs in Guinea-Bissau was distinct, with *S.* Give ST516 being the most commonly isolated serovar and a number of rare STs were found.

Differences in serovar distribution between human and animal populations across countries and regions are common (Hendriksen *et al.* 2011), and may come from the introduction of differing organisms through international travel, human migration, food sources, animal feed, and live-stock trade (Clark *et al.* 1973; Crump, Griffin and Angulo 2002; Aarestrup *et al.* 2007; Hendriksen *et al.* 2008). Notably, I detected a number of households in both Senegal and Guinea-Bissau in which household members had the same serovar/ST, suggesting transmission between household members or infection from the same source. If these organisms are transmitted within the household it may arise during illness, in the convalescence phase, or through animal-to-human

transmission due to close contact with domestic animals. Secondary transmission of the bacteria is typically associated with poor personal hygiene, and *Salmonella* have been shown to survive in various environmental sites at home, which can potentially cause outbreaks (Barker and Bloomfield 2000). Public health interventions should focus on improving hygiene and sanitary conditions at the household level to limit the spread of bacterial infections.

In chapter 5, I showed that *S.* Enteritidis ST11 and *S.* Typhimurium ST19 were associated with bacteremia in Senegal, while *S.* Typhimurium ST313 and ST19, *S.* Choleraesuis ST145 and *S.* Enteritidis ST11 were the common causes of bloodstream infections in Guinea-Bissau. In this study, however, almost all NTS isolates from stool samples in the general population of Senegal and Guinea-Bissau were genetically unrelated to the organisms causing iNTS disease in these countries. This observation could be attributed to low prevalence of asymptomatic infection in the general population, a short duration of asymptomatic carriage, intermittent shedding of iNTS organisms, and/or the low sensitivity of stool culture. Though patients infected with NTS are more frequently likely to develop convalescent carriage than those with typhoid fever, the maximum duration of asymptomatic excretion is generally shorter with NTS organisms in comparison with *S.* Typhi infections (Gunn *et al.* 2014). It is necessary for future investigation of iNTS diseases to include a longitudinal follow-up period of patients to better understand the prevalence of asymptomatic carriers, calculate the duration of carriage, and assess the role of carriage in the transmission of the infecting bacteria.

During this work I additionally detected an *S.* Enteritidis ST11 isolate carrying the IncF

virulence plasmid, which was from a stool specimen of a 29-year-old female from Senegal. The presence of this isolate in this stool sample may be associated with a recent symptomatic infection followed by convalescent shedding of the infecting organism, or it may merely be a sub-clinical infection episode. However, because stool samples were collected on one occasion and health status was not assessed upon enrolment, it is impossible to determine if the person had a symptomatic infection or not.

As opposed to invasive *S*. Typhimurium ST313, which has been dominated by a single lineage (Lineage II), there are multiple lineages of *S*. Enteritidis ST11 circulating in Africa that can cause bloodstream infections (Feasey *et al.* 2016). By inserting the lone *S.* Enteritidis ST11 stool isolate from Senegal into the global phylogenetic structure of *S.* Enteritis ST11, I found that this isolate belonged within the Outlier Cluster, which has been associated with both enterocolitis in Europe/US and bacteraemia in Africa. The precise role of this NTS shedder and their potential for causing symptomatic infections and facilitating transmission cannot be elucidated due to study limitations. However, the integration of genomics and phylogenetics analyses with conventional epidemiology of NTS shedding in Africa is potentially a powerful approach with highly detailed resolution that can be exploited in future research.

Lastly, I also assessed the AMR gene content and plasmid distribution in the NTS organisms from asymptomatic infections in Senegal and Guinea-Bissau. In both locations, I found several MDR *Salmonella* serovars, including *S*. Agona ST13, *S*. Chester ST1954, *S*. Hadar ST33; notably I observed an *S*. Agona that had multiple mutations in the QRDR regions of *gyrA* and *parC*. This observation provides some

further insight into the emergence and spread of MDR *Salmonella* serovars in Africa. *S.* Agona has a wide host-range, is associated with multi-country outbreaks of foodborne infections, and has been frequently isolated from human infections in Latin America (top three most common NTS), Europe (ranked 7th), and North America (rank 13th) (Clark *et al.* 1973; Hendriksen *et al.* 2011), which are possibly linked to read-to-eat food. In various African countries, *S.* Agona, *S.* Chester, and *S.* Hadar are commonly isolated from poultry, poultry products, pig, sheep and food products (Aissa *et al.* 2007; Dione *et al.* 2011a; Molla, Alemayehu and Salah 2011; Kagambèga *et al.* 2013; Gelaw, Nthaba and Matle 2018). The high prevalence of these MDR *Salmonella* serovars in various food sources may pose a threat to food safety and human health. The epidemiology of NTS is complicated and needs to be systematically monitored to identify the trends in epidemiology and to identify the clinically important serovars that may have a major impact on farming industries and public health.

In conclusion, I identified a broad diversity of NTS serovar/STs in asymptomatic stool samples taken from the general human population in Senegal and Guinea-Bissau. I observed only one overlapping *Salmonella* serovar between these two countries, suggesting that these locations have a distinct collection of *Salmonella* serovars/STs. I detected the same organism in multiple individuals in the same household, which may be linked to poor hygiene within the household or a common source of infection in the community. The close monitoring of *Salmonella,* particularly MDR *Salmonella* through a comprehensive one health approach is needed to better understand the transmission dynamics of these complex organisms so we can begin to develop strategies to prevent their circulation.

Chapter 7 General discussion

My work confirms some previous observations with respect to into invasive *Salmonella* disease in Africa, whilst additionally providing new epidemiological insights through the use of WGS. In chapter I confirmed the association between malaria, malnutrition, and anaemia with iNTS disease in young African children. I suggest that a more integrated approach through public health system, which encompass improved hygiene and sanitation, better childhood nutrition, and active case detection of malaria in children are essential to limit the impact of iNTS disease. Although various predisposing risk factors for iNTS disease have been progressively elucidated, we have limited knowledge regarding the immunological mechanisms triggered by *plasmodium* infections, malnutrition, and HIV that make iNTS permissive. Further research is required to better understand the relationship between the underlying health conditions of individuals with various comorbidities and iNTS disease. This focus may be particularly important in many tropical countries with high burdens of malaria, HIV, and an increased risk of water-borne diseases

In combination with differing MDR iNTS organisms, MDR *S.* Typhi are also present in sub-Saharan Africa. According to my findings, MDR typhoid fever is highly pervasive in both West and East Africa; this situation may be further exacerbated by a global increase in resistance to other important antimicrobial classes for treating typhoid fever such as the fluoroquinolones and third generation cephalosporins. In addition, I was able to show that the *S.* Typhi population in Africa has been shaped by multiple introductions of MDR H58 (4.3.1). *S.* Typhi has been introduced on several occasions into Eastern and Southern Africa from South Asia. These introductions have instigated

numerous local clonal expansions and intra-regional transmission. Continued and strengthened continent wide surveillance of MDR typhoid fever exploiting WGS is essential to further evaluate and monitor the trends of AMR in *S.* Typhi. These data will enable the provision of updated treatment guidelines and the identification of at-risk groups or/and areas for progressive public health measures. In the countries where a high burden of MDR typhoid fever was identified I advocate the implementation of TCVs, while longer-term commitments and efforts are required to improve water, sanitation, and hygiene conditions at both a national and international level.

The emergence and spread of MDR iNTS in Africa has been reported previously, particularly for *S.* Typhimurium ST313 and *S.* Enteritidis ST11. However, there has been insufficient data regarding the geographical distribution of predominant iNTS genotypes-serovars and their AMR trends and the population-based incidence of MDR iNTS disease in Africa has not been estimated. I found a preponderance and continued spread of MDR *S.* Typhimurium ST313 and MDR *S.* Enteritidis ST11 across West, East and South-eastern Africa. Furthermore, I found that MDR *S.* Dublin ST10 has also emerged in West Africa, which warrants close monitoring. The further detection of reduced fluoroquinolones susceptibility in MDR *S.* Typhimurium ST313 and *S.* Enteritidis ST11, and resistance to third generation cephalosporins in *S.* Typhimurium ST313 from East Africa poses a significant concern about the increasing trend in resistance against newer antimicrobials. While further surveillance that monitors iNTS disease and the corresponding AMR profiles of the infecting organism are needed in these endemic communities, more research on the circulation of these pathogens in animals and the environment are also required to understand the transmission pathways of NTS organisms. Additionally, assessing the antimicrobial usage in food, animal

husbandry, human communities, and healthcare facilities are also important for understanding the factors driving the emergence MDR NTS in Africa. Considering the high burden of MDR iNTS disease among young children in multiple sub-Saharan African countries and the co-circulation of several MDR iNTS serovars, there is a very strong argument for the development and deployment of a multivalent vaccine targeting the predominant iNTS serovars.

There is paucity of data regarding the transmission dynamics of the NTS serovars associated with gastroenteritis and iNTS disease in Africa. Understanding the potential infectivity of NTS and their excretion from humans may be important for future disease control efforts. I conducted a molecular investigation of limited number of NTS organisms from a sub-set of asymptomatic individual residing in two distinct African communities. Individuals shedding NTS organisms may contribute to the transmission of organisms and an increased disease burden. I noted that *S.* Typhimurium ST313 and *S.* Enteritidis ST11 are seldom detected in stools from the general population, which suggests either that these organisms are not associated with asymptomatic disease or they have a limited duration of shedding. However, I isolated a lone *S.* Enteritidis ST11 carrying a virulence plasmid from a 29-year-old woman with a sub-clinical infection. To further understand the transmission of NTS in Africa, future investigations should include follow-up periods of at least one year for iNTS cases, their household contacts, and the local environment to determine the role of carrier, measure the shedding period, and provide more detailed characteristics of the transmission cycle(s) of iNTS/NTS disease.

Lastly, although there is significant burden of typhoid fever and iNTS disease in sub-

Saharan African, there is paucity of data regarding disease severity, clinical symptoms and complications. Severe complications from enteric fever have been investigated in several studies in Asia; gastrointestinal bleeding, perforation, and encephalopathy were recorded among hospitalized patients. However, such data is scarce in Africa and I predict the rate of complications may be high given the burden of AMR pathogens, a high prevalence of malnutrition, the co-circulation of malaria and HIV, limited access to health facilities, and unsatisfactory public health services. Research to understand the severity and complication rate of invasive *Salmonella* disease, especially at a community level to identify attributable risk factors are required for better management and control of this group of important diseases.

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Chapter 9 Appendices

9.1. All invasive *Salmonella* species analysed in Chapter 3

9.2 All *S.* Typhi organisms analysed in Chapter 4

9.3 All iNTS organisms analysed in Chapter 5

9.4 All NTS organisms analysed in Chapter 6

9.5 Publications during DPhil candidature

9.1. All invasive *Salmonella* species analysed in Chapter 3

See Chapter 3 Table 3.1.

9.2 All *S.* Typhi organisms analysed in Chapter 4

	Burkina Faso	**Ethiopia** (Butajira)	**Ghana**	**Guinea-Bissau** (Bandim)	**Kenya** (Kibera)	**Madagascar**	**Senegal** (Pikine)	**South Africa**	**Tanzania**	**Uganda**	**Gambia**
Isolates analysed for this study[1] (249 *S.* Typhi)	**14**	**2**	**101**	**3**	**59**	**8**	**8**	**2**	**11**	**30**	**11**
	11 (Polesgo) 3 (NiokoII)	2	30 (TSAP) 11 (TSAP; outside catchment area) 22 (TSAP; >15yrs) 6 ("IsolateAgogo") 32 (unidentified)	3	59	6 (Imerintsiatosika) 2 (Isotry)	8	2	6 MU[4] 4 MR[5] 1 MO[6]		
TSAP[2] (135 *S.* Typhi)	**18**	**3**	**30**	**3**	**54**	**9**	**7**	**2**	**9**	n.a.	n.a.
	13 (Polesgo) 5 (NiokoII)	3	30 (AAN)[3]	3	54	6 (Imerintsiatosika) 3 (Isotry)	7	2	6 (18) MU[4] 3 (6) MR[5]	n.a.	n.a.
Other_Ghana[7]	n.a.	n.a.	6 ("IsolateAgogo") 32 (unidentified)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other_Uganda	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	30	n.a.
Other_Gambia	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	11

Footnote: Reproduced from Park *et al.* (2018)

[1] Total 249 *S.* Typhi organisms were analysed for this study: 208 *S.* Typhi isolates from TSAP and other Ghana projects; 30 *S.* Typhi from Uganda; and 11 *S.* Typhi from Gambia.

[2] TSAP recruited 13,558 patients from 13 sites in 10 countries meeting the study inclusion criteria, of which 127 patients were excluded due to incomplete dataset. This resulted in 13,431 patients and 135 *S.* Typhi found in 9 countries for analysis.(Marks *et al.* 2017) No *S.* Typhi was found from Sudan. The differences in the number of *S.* Typhi in TSAP publication (total 135 *S.* Typhi in Marks et al) and the isolates analysed for this manuscript (total 249 *S.* Typhi, including 208 *S.* Typhi from TSAP and other Ghana projects, 30 and 11 *S.* Typhi organisms from Uganda and Gambia, respectively) are due to several factors listed below:

- Kenya, Senegal, and Tanzania: *S.* Typhi cases, which did not meet the catchment area or fever recruitment criteria, were excluded in the final analysis in the TSAP publication but included in this bacterial genomic analysis.
- Burkina Faso, Ethiopia, and Madagascar: S. Typhi isolates analysed for this study are based on the whole genome sequencing result and quality control screening.
- Ghana: 30 *S.* Typhi isolates from under 15 years of age were presented in TSAP publication. Additionally, 11 isolates from TSAP but not meeting the catchment area criteria, 22 isolates from TSAP but above 15 years of age, 6 isolates from "IsolateAgogo" dataset, and 32 isolates from non-TSAP projects in Ghana ("FISA", "TYSA", and "IsolateAgogo") have been added to this analysis.

[3] AAN: Asante Akim North

[4] MU: Moshi Urban

[5] MR: Moshi Rural

[6] MO: Moshi Other (This 1 case was out of the TSAP catchment area; 21 year old patient enrolled with *S.* Typhi infection.)

[7] Other_Ghana: *S.* Typhi isolates from non-TSAP projects in Ghana ("Febrile Illnesses Surveillance in Africa (FISA)", "Typhoid Surveillance in Africa (TYSA)", and "IsolateAgogo" datasets)

9.2.1 Metadata of whole genome sequenced *S.* Typhi isolates from my and published data

Metadata of 249 *S.* Typhi isolates from my data sorted alphabetically by country

Lane_ID	Study_ID	Source	Year	Continent	Region_within _continent	Country	New genotype
16404_4#10	bkf01465	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	2.2
16404_4#11	bkf01760	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	3.1.1
16404_4#35	bkf00126	THIS_STUDY_IVI	2012	Africa	West_Africa	BurkinaFaso	3.1.1
16404_4#38	bkf001628	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	2.3.2
16404_4#41	bkf00258	THIS_STUDY_IVI	2012	Africa	West_Africa	BurkinaFaso	4.1.1
16404_4#57	bkf01146	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	4.1.1
16404_4#63	bfk01783	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	3.1.1
16404_4#70	bkf01464	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	3.1.1
16404_4#77	bkf01493	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	3.1.1
16549_7#11	bkf01613	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	3.1.1
16549_7#15	bkf01660	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	3.1.1
16549_7#22	bkf00319	THIS_STUDY_IVI	2012	Africa	West_Africa	BurkinaFaso	3.1.1
16549_7#7	bkf01043	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	2.2
16549_7#8	bkf01755	THIS_STUDY_IVI	2013	Africa	West_Africa	BurkinaFaso	2.3.2
16399_4#54	eth00410	THIS_STUDY_IVI	2012	Africa	East_Africa	Ethiopia	1.2
16399_4#80	eth00717	THIS_STUDY_IVI	2013	Africa	East_Africa	Ethiopia	2.2.2
17225_4#35	NA	THIS_STUDY_GAMBIA	2014	Africa	West_Africa	Gambia	2.3.2
17225_4#39	NA	THIS_STUDY_GAMBIA	2011	Africa	West_Africa	Gambia	2.3.2
17225_4#42	NA	THIS_STUDY_GAMBIA	2013	Africa	West_Africa	Gambia	2.3.2
17225_4#47	NA	THIS_STUDY_GAMBIA	2012	Africa	West_Africa	Gambia	2.3.2
17225_4#49	NA	THIS_STUDY_GAMBIA	2010	Africa	West_Africa	Gambia	2.3.2
17225_4#54	NA	THIS_STUDY_GAMBIA	2014	Africa	West_Africa	Gambia	2.3.2

17225_4#58	NA	THIS_STUDY_GAMBIA	2012	Africa	West_Africa	Gambia	2.3.2
17225_4#59	NA	THIS_STUDY_GAMBIA	2008	Africa	West_Africa	Gambia	2.3.2
17225_4#61	NA	THIS_STUDY_GAMBIA	2013	Africa	West_Africa	Gambia	2.3.2
17225_4#65	NA	THIS_STUDY_GAMBIA	2012	Africa	West_Africa	Gambia	2.3.2
17225_4#66	NA	THIS_STUDY_GAMBIA	2008	Africa	West_Africa	Gambia	2.3.2
16399_3#10	gha914222	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	2.3.2
16399_3#12	gha58918	THIS_STUDY_IVI_"IsolateAgogo"	2007	Africa	West_Africa	Ghana	3.1.1
16399_3#2	gha75193	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16399_3#26	gha87249	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16399_4#16	gha500316	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16399_4#26	gha130010	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16399_4#32	gha917800	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16399_4#6	gha98375	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	0.0.3
16399_4#70	gha80759	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16399_4#78	gha53002	THIS_STUDY_IVI_"IsolateAgogo"	2007	Africa	West_Africa	Ghana	3.1.1
16399_4#85	gha52446	THIS_STUDY_IVI_"IsolateAgogo"	2007	Africa	West_Africa	Ghana	3.1.1
16404_4#19	gha9728	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_4#47	gha112792	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_4#81	gha112987	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_4#88	gha115200	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#11	gha300005	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_5#13	gha500820	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#2	gha112543	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_5#23	gha300884	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_5#29	gha400648	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_5#33	gha500212	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#4	gha115082	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#41	gha115343	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#50	gha400630	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1

16404_5#55	gha115531	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#57	gha500362	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#6	gha116178	THIS_STUDY_IVI	2012	Africa	West_Africa	Ghana	3.1.1
16404_5#64	gha400543	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_5#65	gha500347	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#7	gha113010	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_5#71	gha300795	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_5#78	gha115524	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	2.3.2
16404_5#79	gha116073	THIS_STUDY_IVI	2012	Africa	West_Africa	Ghana	3.1.1
16404_5#81	gha115752	THIS_STUDY_IVI	2012	Africa	West_Africa	Ghana	3.1.1
16404_5#83	gha500707	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#88	gha115138	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#90	gha114070	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_5#91	gha500926	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_6#12	gha80509	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#13	gha98552	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#27	gha52234	THIS_STUDY_IVI_"IsolateAgogo"	2007	Africa	West_Africa	Ghana	3.1.1
16404_6#33	gha114149	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_6#46	gha78920	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#52	gha87039	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	0.0.3
16404_6#53	gha77941	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	2.3.2
16404_6#56	gha98311	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#58	gha89541	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#63	gha66994	THIS_STUDY_IVI_"IsolateAgogo"	2008	Africa	West_Africa	Ghana	3.1.1
16404_6#67	gha300947	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16404_6#68	gha89997	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#70	gha75716	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#71	gha68564	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#72	gha85372	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	2.3.2

16404_6#76	gha7119	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#78	gha73406	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#79	gha113834	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16404_6#89	gha91946	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_6#9	gha200791	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#12	gha113411	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#26	gha112905	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	2.3.2
16549_7#33	gha500763	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#35	gha300113	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#36	gha400509	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#42	gha113055	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	2.3.2
16549_7#43	gha400010	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#45	gha115685	THIS_STUDY_IVI	2012	Africa	West_Africa	Ghana	3.1.1
16549_7#46	gha113825	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#49	gha115045	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#51	gha113597	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#52	gha114569	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#55	gha115454	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#56	gha114899	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#57	gha114578	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#62	gha500517	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	4.1
16549_7#65	gha300372	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#69	gha400019	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#71	gha500326	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#78	gha115475	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#79	gha114380	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	2.3.2
16549_7#80	gha114349	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	2.3.2
16549_7#83	gha112722	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_7#84	gha114025	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1

16549_7#87	gha114762	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_7#89	gha114627	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16549_7#91	gha113472	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_8#12	gha115381	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#15	gha114347	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#22	gha115603	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#23	gha500849	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#27	gha300680	THIS_STUDY_IVI	2010	Africa	West_Africa	Ghana	3.1.1
16549_8#30	gha400617	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16549_8#4	gha116092	THIS_STUDY_IVI	2012	Africa	West_Africa	Ghana	3.1.1
16549_8#45	gha910293	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16549_8#46	gha200784	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#5	gha114044	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#59	gha60484	THIS_STUDY_IVI_"IsolateAgogo"	2007	Africa	West_Africa	Ghana	0.0.1
16549_8#6	gha114027	THIS_STUDY_IVI	2011	Africa	West_Africa	Ghana	3.1.1
16549_8#74	gha601491	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16549_8#80	gha91708	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16549_8#82	gha916885	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16549_8#84	gha75916	THIS_STUDY_IVI	Unknown	Africa	West_Africa	Ghana	3.1.1
16404_4#44	gnb01556	THIS_STUDY_IVI	2013	Africa	West_Africa	GuineaBissau	2.3.2
16404_4#61	gnb00286	THIS_STUDY_IVI	2012	Africa	West_Africa	GuineaBissau	2.3.2
16549_7#3	gnb00358	THIS_STUDY_IVI	2012	Africa	West_Africa	GuineaBissau	2.3.1
16404_4#39	2013117808	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16404_4#46	2011740872	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#5	2011731737	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#53	2011750677	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#59	2011750771	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#65	2011745945	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16404_4#66	2011731485	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1

16404_4#73	2012106455	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#75	2012113075	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#80	2011741885	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#82	2012113125	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#87	2011731763	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#89	2012119497	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16404_5#35	2011731482	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#36	2011751132	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#37	2011731303	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#43	2011731566	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#44	2011751364	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#45	2011745646	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16404_5#51	2011732483	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#52	2011731699	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#53	2011750411	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#59	2012113910	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#60	2011740790	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#61	2011741567	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#67	2010758602	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#68	2011736351	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#69	2013122084	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16404_5#75	2011732466	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#76	2011750601	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#77	2011731267	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#84	2011751738	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_5#85	2012113059	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_6#3	2011736425	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_6#35	2012113041	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_7#18	2010758257	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1

16549_7#20	2011751973	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_7#23	2011751050	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_7#4	2012106621	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_7#5	2013118144	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16549_8#1	2011740814	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#10	2011741744	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#16	2010758347	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#17	2011740612	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#18	2011752087	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#2	2011740533	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#25	2011741582	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#26	2011751208	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#31	2011747401	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16549_8#33	2011750428	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#34	2013115453	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16549_8#47	2011751233	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#48	2011731796	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#54	2011750383	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#63	2011752322	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#7	2013117358	THIS_STUDY_IVI	2013	Africa	East_Africa	Kenya	4.3.1
16549_8#71	2012113780	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#8	2011731274	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16549_8#9	2010758424	THIS_STUDY_IVI	2012	Africa	East_Africa	Kenya	4.3.1
16404_4#37	mgr00360	THIS_STUDY_IVI	2011	Africa	East_Africa_Island	Madagascar	2.2
16404_4#51	mgr00332	THIS_STUDY_IVI	2011	Africa	East_Africa_Island	Madagascar	2.5
16404_4#52	mgr03169	THIS_STUDY_IVI	2013	Africa	East_Africa_Island	Madagascar	2.5
16404_4#58	mgr00361	THIS_STUDY_IVI	2011	Africa	East_Africa_Island	Madagascar	2.2
16404_4#64	mgr00374	THIS_STUDY_IVI	2012	Africa	East_Africa_Island	Madagascar	2.5
16404_4#78	mgr02174	THIS_STUDY_IVI	2012	Africa	East_Africa_Island	Madagascar	4.1

16549_7#16	mgr03238	THIS_STUDY_IVI	2013	Africa	East_Africa_Island	Madagascar	2.2
16549_7#17	mgr00638	THIS_STUDY_IVI	2012	Africa	East_Africa_Island	Madagascar	2.5
16404_4#1	sen00740	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	2.3.2
16404_4#42	sen00569	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	2.3.2
16404_4#6	sen00651	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	4.1
16404_4#8	sen01167	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	2.3.2
16404_4#9	sen00277	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	2.3.2
16404_4#90	sen00496	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	3.1
16549_7#21	sen00329	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	2.3.2
16549_7#6	sen00087	THIS_STUDY_IVI	2012	Africa	West_Africa	Senegal	2.3.2
16404_4#40	rsa692502	THIS_STUDY_IVI	Unknown	Africa	South_Africa	South Africa	3.3.1
16404_4#48	rsa639624	THIS_STUDY_IVI	Unknown	Africa	South_Africa	South Africa	3.3.1
16399_3#52	tzn05836	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
16399_3#68	tzn05707	THIS_STUDY_IVI	2011	Africa	East_Africa	Tanzania	4.3.1
16399_4#23	tzn05829	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
16399_4#37	tzn05256	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
16399_4#42	tzn05856	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
16399_4#46	tzn06112	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
16399_4#52	tzn05915	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
16399_4#56	tzn05005	THIS_STUDY_IVI	2011	Africa	East_Africa	Tanzania	4.3.1
16399_4#61	tzn04978	THIS_STUDY_IVI	2011	Africa	East_Africa	Tanzania	4.3.1
16399_4#69	tzn05137	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	2.2.2
16399_4#75	tzn05833	THIS_STUDY_IVI	2012	Africa	East_Africa	Tanzania	4.3.1
19787_3#1	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#10	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#11	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#12	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#13	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#14	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1

19787_3#15	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#16	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#17	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#18	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#19	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#2	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#20	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#21	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#22	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#23	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#24	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#25	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#26	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#27	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#28	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#29	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#3	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#30	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#4	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#5	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#6	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#7	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#8	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1
19787_3#9	NA	THIS_STUDY_UGANDA	2015	Africa	East_Africa	Uganda	4.3.1

Metadata of published global collection of *S.* Typhi isolates sorted alphabetically by continent

Reproduced from Wong *et al.* (2015): Global collection of 2,057 *S.* Typhi isolates.

Lane_ID	Source	Year	Accession numbers	Continent	Country	New genotype
10060_6#69	GLOBAL	2006	ERR331366	Africa	Tanzania	2.2.2
10060_6#71	GLOBAL	2008	ERR331368	Africa	Tanzania	4.3.1
10060_6#72	GLOBAL	2008	ERR331369	Africa	Tanzania	4.3.1
10060_6#73	GLOBAL	2006	ERR331370	Africa	Tanzania	2.2.0
10060_6#74	GLOBAL	2007	ERR331371	Africa	Tanzania	3.3.1
10060_6#75	GLOBAL	2008	ERR331372	Africa	Tanzania	4.3.1
10060_6#76	GLOBAL	2007	ERR331373	Africa	Tanzania	3.1.0
10060_6#77	GLOBAL	2008	ERR331374	Africa	Tanzania	4.3.1
10060_6#78	GLOBAL	2008	ERR331375	Africa	Tanzania	4.3.1
10060_6#79	GLOBAL	2008	ERR331376	Africa	Tanzania	4.3.1
10060_6#80	GLOBAL	2008	ERR331377	Africa	Tanzania	4.3.1
10060_6#81	GLOBAL	2008	ERR331378	Africa	Tanzania	4.3.1
10060_6#82	GLOBAL	2008	ERR331379	Africa	Tanzania	4.3.1
10060_6#83	GLOBAL	2008	ERR331380	Africa	Tanzania	4.3.1
10060_6#84	GLOBAL	2006	ERR331381	Africa	Tanzania	2.2.0
10071_3#22	GLOBAL	2007	ERR337998	Africa	S.Africa	2.4.1
10071_3#23	GLOBAL	2006	ERR337999	Africa	S.Africa	2.5.0
10071_3#25	GLOBAL	2006	ERR338001	Africa	S.Africa	2.4.0
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10071_3#28	GLOBAL	2004	ERR338004	Africa	S.Africa	4.1.1
10071_3#29	GLOBAL	2005	ERR338005	Africa	S.Africa	2.4.0
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10071_3#40	GLOBAL	2006	ERR338016	Africa	S.Africa	2.4.1
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10071_8#68	GLOBAL	2007	ERR338137	Africa	Kenya	4.3.1
10071_8#69	GLOBAL	2007	ERR338138	Africa	Kenya	4.3.1
10071_8#70	GLOBAL	2008	ERR338139	Africa	Kenya	4.3.1
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10071_8#72	GLOBAL	2007	ERR338141	Africa	Kenya	4.3.1
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10071_8#76	GLOBAL	2007	ERR338145	Africa	Kenya	4.3.1
10071_8#77	GLOBAL	2007	ERR338146	Africa	Kenya	4.3.1
10071_8#78	GLOBAL	2008	ERR338147	Africa	Kenya	4.3.1
10071_8#79	GLOBAL	2007	ERR338148	Africa	Kenya	4.3.1
10071_8#80	GLOBAL	2007	ERR338149	Africa	Kenya	4.3.1
10071_8#81	GLOBAL	2007	ERR338150	Africa	Kenya	4.3.1
10071_8#82	GLOBAL	2008	ERR338151	Africa	Kenya	4.3.1
10071_8#83	GLOBAL	2007	ERR338152	Africa	Kenya	4.3.1
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10071_8#91	GLOBAL	2008	ERR338160	Africa	Kenya	4.3.1
10071_8#92	GLOBAL	2008	ERR338161	Africa	Kenya	4.3.1
10071_8#93	GLOBAL	2009	ERR338162	Africa	Kenya	3.3.1
10071_8#94	GLOBAL	2008	ERR338163	Africa	Kenya	4.3.1

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10349_1#88	GLOBAL	2000	ERR343336	Africa	Morocco	#N/A
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10426_1#4	GLOBAL	2010	ERR349526	Africa	DRC	2.5.1
10426_1#5	GLOBAL	2010	ERR349527	Africa	DRC	2.5.1
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10540_1#5	GLOBAL	2011	ERR352602	Africa	DRC	2.5.1
10540_1#7	GLOBAL	2011	ERR352604	Africa	DRC	2.5.1
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10561_2#17	GLOBAL	2010	ERR357592	Africa	DRC	2.5.1
10561_2#21	GLOBAL	2010	ERR357596	Africa	DRC	2.5.1
10561_2#29	GLOBAL	2010	ERR357604	Africa	DRC	2.5.1
10561_2#35	GLOBAL	2011	ERR357610	Africa	DRC	2.5.1
10561_2#4	GLOBAL	2011	ERR357579	Africa	DRC	2.5.1
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10592_2#42	GLOBAL	1998	ERR360490	Africa	Gabon	3.3.0

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10592_2#49	GLOBAL	2002	ERR360497	Africa	Comoros	2.5.0
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10592_2#58	GLOBAL	2009	ERR360506	Africa	CAR	2.5.1
10592_2#59	GLOBAL	1999	ERR360507	Africa	Mali	2.3.2
10592_2#61	GLOBAL	1980	ERR360509	Africa	Madagascar	2.2.0
10592_2#63	GLOBAL	1976	ERR360511	Africa	DRC	1.1.3
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10593_2#19	GLOBAL	2006	ERR360632	Africa	BurkinaFaso	3.1.1
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13097_1#78	NIGERIA	2009	ERR573942	Africa	Nigeria: Abuja	2.3.1
13097_1#79	NIGERIA	2009	ERR573943	Africa	Nigeria: Abuja	3.1.1
13097_1#80	NIGERIA	2009	ERR573944	Africa	Nigeria: Abuja	3.1.1
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13097_1#83	NIGERIA	2009	ERR573947	Africa	Nigeria: Abuja	3.1.1
13097_1#84	NIGERIA	2009	ERR573948	Africa	Nigeria: Abuja	3.1.1
13097_1#85	NIGERIA	2009	ERR573949	Africa	Nigeria: Abuja	3.1.1
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13103_1#12	NIGERIA	2010	ERR573960	Africa	Nigeria: Abuja	3.1.1
13103_1#13	NIGERIA	2010	ERR573961	Africa	Nigeria: Abuja	0.0.3
13103_1#2	NIGERIA	2009	ERR573950	Africa	Nigeria: Abuja	3.1.1
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9953_5#77	GLOBAL	2010	ERR326673	Asia	Laos	3.4.0
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9953_5#9	GLOBAL	2009	ERR326605	Asia	Indonesia	4.1.0
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Salmonella_enterica_subsp_enterica _serovar_Typhi_str_CR0044_v1	GLOBAL	2007	SalTypSTCR0044 1.0	Asia	Malaysia	#N/A
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Salmonella_enterica_subsp_enterica _serovar_Typhi_str_J185_v1	GLOBAL	1985	ASM18031v1	Asia	Indonesia	#N/A
Salmonella_enterica_subsp_enterica _serovar_Typhi_str_P_stx_12_v1	GLOBAL	2012	ASM24553v1	Asia	India	4.3.1
Salmonella_enterica_subsp_enterica _serovar_Typhi_str_ST0208_v1	GLOBAL	2008	YKP860805.1	Asia	Malaysia	#N/A
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10561_2#49	GLOBAL	2012	ERR357624	AustraliaandOceania	Samoa	3.5.4
10561_2#52	GLOBAL	2012	ERR357627	AustraliaandOceania	Samoa	3.5.4
10561_2#56	GLOBAL	2012	ERR357631	AustraliaandOceania	Samoa	2.2.1
10562_2#26	GLOBAL	2010	ERR357781	AustraliaandOceania	Samoa	3.5.4
10562_2#3	GLOBAL	2009	ERR357758	AustraliaandOceania	Samoa	3.5.4
10562_2#4	GLOBAL	2010	ERR357759	AustraliaandOceania	Samoa	3.5.4
10562_2#43	GLOBAL	1992	ERR357798	AustraliaandOceania	PapuaNewGuinea	2.1.7
10562_2#44	GLOBAL	2008	ERR357799	AustraliaandOceania	Samoa	3.5.4
10562_2#45	GLOBAL	1980	ERR357800	AustraliaandOceania	PapuaNewGuinea	4.1.0
10562_2#46	GLOBAL	1981	ERR357801	AustraliaandOceania	Fiji	4.2.1
10562_2#47	GLOBAL	1991	ERR357802	AustraliaandOceania	Vanuatu	4.1.0

10562_2#48	GLOBAL	1992	ERR357803	AustraliaandOceania	Fiji	4.3.1
10562_2#49	GLOBAL	1993	ERR357804	AustraliaandOceania	PapuaNewGuinea	2.1.7
10562_2#5	GLOBAL	2011	ERR357760	AustraliaandOceania	Samoa	3.5.4
10562_2#50	GLOBAL	1993	ERR357805	AustraliaandOceania	Fiji	2.3.5
10562_2#51	GLOBAL	1984	ERR357806	AustraliaandOceania	Fiji	4.2.1
10562_2#52	GLOBAL	1993	ERR357807	AustraliaandOceania	Fiji	4.3.1
10562_2#53	GLOBAL	1985	ERR357808	AustraliaandOceania	Fiji	2.3.5
10562_2#54	GLOBAL	1986	ERR357809	AustraliaandOceania	PapuaNewGuinea	4.1.0
10562_2#55	GLOBAL	1994	ERR357810	AustraliaandOceania	PapuaNewGuinea	2.1.7
10562_2#56	GLOBAL	1996	ERR357811	AustraliaandOceania	PapuaNewGuinea	2.1.7
10562_2#61	GLOBAL	2011	ERR357816	AustraliaandOceania	Samoa	3.5.4
10562_2#80	GLOBAL	2012	ERR357835	AustraliaandOceania	Samoa	3.5.4
10562_2#84	GLOBAL	2012	ERR357839	AustraliaandOceania	Samoa	3.5.4
10562_2#85	GLOBAL	2012	ERR357840	AustraliaandOceania	Samoa	3.5.4
10562_2#86	GLOBAL	2011	ERR357841	AustraliaandOceania	Fiji	3.3.1
10562_2#9	GLOBAL	2012	ERR357764	AustraliaandOceania	Australia_no_travel	4.3.1
8447_8#1	GLOBAL	2008	ERR204244	AustraliaandOceania	Fiji	4.2.1
8447_8#10	GLOBAL	2008	ERR204253	AustraliaandOceania	Fiji	4.2.1
8447_8#11	GLOBAL	2008	ERR204254	AustraliaandOceania	Fiji	4.2.2
8447_8#12	GLOBAL	2008	ERR204255	AustraliaandOceania	Fiji	4.2.1
8447_8#13	GLOBAL	2008	ERR204256	AustraliaandOceania	Fiji	4.2.1
8447_8#14	GLOBAL	2008	ERR204257	AustraliaandOceania	Fiji	4.2.1
8447_8#15	GLOBAL	2008	ERR204258	AustraliaandOceania	Fiji	4.2.1
8447_8#16	GLOBAL	2008	ERR204259	AustraliaandOceania	Fiji	4.2.1
8447_8#17	GLOBAL	2008	ERR204260	AustraliaandOceania	Fiji	4.2.2
8447_8#18	GLOBAL	2008	ERR204261	AustraliaandOceania	Fiji	4.2.2
8447_8#19	GLOBAL	2008	ERR204262	AustraliaandOceania	Fiji	4.2.2
8447_8#2	GLOBAL	2008	ERR204245	AustraliaandOceania	Fiji	4.2.1
8447_8#20	GLOBAL	2008	ERR204263	AustraliaandOceania	Fiji	4.2.2

8447_8#21	GLOBAL	2008	ERR204264	AustraliaandOceania	Fiji	4.2.2
8447_8#22	GLOBAL	2008	ERR204265	AustraliaandOceania	Fiji	4.2.2
8447_8#23	GLOBAL	2008	ERR204266	AustraliaandOceania	Fiji	4.2.2
8447_8#24	GLOBAL	2008	ERR204267	AustraliaandOceania	Fiji	4.2.2
8447_8#26	GLOBAL	2008	ERR204269	AustraliaandOceania	Fiji	4.2.2
8447_8#27	GLOBAL	2008	ERR204270	AustraliaandOceania	Fiji	4.2.1
8447_8#28	GLOBAL	2008	ERR204271	AustraliaandOceania	Fiji	4.2.1
8447_8#29	GLOBAL	2008	ERR204272	AustraliaandOceania	Fiji	4.2.2
8447_8#3	GLOBAL	2008	ERR204246	AustraliaandOceania	Fiji	4.2.2
8447_8#30	GLOBAL	2008	ERR204273	AustraliaandOceania	Fiji	4.2.2
8447_8#31	GLOBAL	2008	ERR204274	AustraliaandOceania	Fiji	4.2.2
8447_8#32	GLOBAL	2008	ERR204275	AustraliaandOceania	Fiji	4.2.2
8447_8#33	GLOBAL	2008	ERR204276	AustraliaandOceania	Fiji	4.2.2
8447_8#4	GLOBAL	2008	ERR204247	AustraliaandOceania	Fiji	4.2.2
8447_8#5	GLOBAL	2008	ERR204248	AustraliaandOceania	Fiji	4.2.1
8447_8#6	GLOBAL	2008	ERR204249	AustraliaandOceania	Fiji	4.2.1
8447_8#7	GLOBAL	2008	ERR204250	AustraliaandOceania	Fiji	4.2.1
8447_8#8	GLOBAL	2008	ERR204251	AustraliaandOceania	Fiji	4.2.2
8447_8#9	GLOBAL	2008	ERR204252	AustraliaandOceania	Fiji	4.2.1
8490_5#1	GLOBAL	2011	ERR213219	AustraliaandOceania	Fiji	4.2.2
8490_5#10	GLOBAL	2011	ERR213228	AustraliaandOceania	Fiji	4.2.2
8490_5#11	GLOBAL	2011	ERR213229	AustraliaandOceania	Fiji	4.2.2
8490_5#12	GLOBAL	2011	ERR213230	AustraliaandOceania	Fiji	4.2.2
8490_5#13	GLOBAL	2011	ERR213231	AustraliaandOceania	Fiji	4.2.2
8490_5#14	GLOBAL	2011	ERR213232	AustraliaandOceania	Fiji	4.2.2
8490_5#15	GLOBAL	2011	ERR213233	AustraliaandOceania	Fiji	4.2.1
8490_5#16	GLOBAL	2011	ERR213234	AustraliaandOceania	Fiji	4.2.2
8490_5#17	GLOBAL	2011	ERR213235	AustraliaandOceania	Fiji	4.2.2
8490_5#18	GLOBAL	2011	ERR213236	AustraliaandOceania	Fiji	4.2.2

8490_5#19	GLOBAL	2011	ERR213237	AustraliaandOceania	Fiji	4.2.2
8490_5#2	GLOBAL	2011	ERR213220	AustraliaandOceania	Fiji	4.2.2
8490_5#20	GLOBAL	2011	ERR213238	AustraliaandOceania	Fiji	4.2.2
8490_5#21	GLOBAL	2011	ERR213239	AustraliaandOceania	Fiji	4.2.2
8490_5#22	GLOBAL	2011	ERR213240	AustraliaandOceania	Fiji	4.2.2
8490_5#23	GLOBAL	2011	ERR213241	AustraliaandOceania	Fiji	4.2.2
8490_5#24	GLOBAL	2011	ERR213242	AustraliaandOceania	Fiji	4.2.2
8490_5#25	GLOBAL	2011	ERR213243	AustraliaandOceania	Fiji	4.2.2
8490_5#26	GLOBAL	2011	ERR213244	AustraliaandOceania	Fiji	4.2.2
8490_5#27	GLOBAL	2011	ERR213245	AustraliaandOceania	Fiji	4.2.2
8490_5#28	GLOBAL	2011	ERR213246	AustraliaandOceania	Fiji	4.2.2
8490_5#29	GLOBAL	2011	ERR213247	AustraliaandOceania	Fiji	4.2.2
8490_5#3	GLOBAL	2011	ERR213221	AustraliaandOceania	Fiji	4.2.2
8490_5#30	GLOBAL	2009	ERR213248	AustraliaandOceania	Fiji	4.2.2
8490_5#31	GLOBAL	2000	ERR213249	AustraliaandOceania	Fiji	4.2.1
8490_5#32	GLOBAL	2000	ERR213250	AustraliaandOceania	Fiji	4.2.1
8490_5#33	GLOBAL	1997	ERR213251	AustraliaandOceania	Fiji	4.2.1
8490_5#34	GLOBAL	1997	ERR213252	AustraliaandOceania	Fiji	4.2.1
8490_5#35	GLOBAL	1996	ERR213253	AustraliaandOceania	Fiji	4.2.0
8490_5#36	GLOBAL	1996	ERR213254	AustraliaandOceania	Fiji	4.2.1
8490_5#4	GLOBAL	2011	ERR213222	AustraliaandOceania	Fiji	4.2.2
8490_5#5	GLOBAL	2011	ERR213223	AustraliaandOceania	Fiji	4.2.2
8490_5#6	GLOBAL	2011	ERR213224	AustraliaandOceania	Fiji	4.2.2
8490_5#7	GLOBAL	2011	ERR213225	AustraliaandOceania	Fiji	4.2.2
8490_5#8	GLOBAL	2011	ERR213226	AustraliaandOceania	Fiji	4.2.2
8490_5#9	GLOBAL	2011	ERR213227	AustraliaandOceania	Fiji	4.2.2
8490_6#37	GLOBAL	1996	ERR213255	AustraliaandOceania	Fiji	4.2.1
8490_6#38	GLOBAL	1996	ERR213256	AustraliaandOceania	Fiji	4.2.1
8490_6#39	GLOBAL	1996	ERR213257	AustraliaandOceania	Fiji	4.2.1

8490_6#40	GLOBAL	1996	ERR213258	AustraliaandOceania	Fiji	4.2.1
8490_6#41	GLOBAL	1996	ERR213259	AustraliaandOceania	Fiji	4.2.1
8490_6#42	GLOBAL	1996	ERR213260	AustraliaandOceania	Fiji	4.2.3
8490_6#43	GLOBAL	1996	ERR213261	AustraliaandOceania	Fiji	4.2.3
8490_6#44	GLOBAL	1996	ERR213262	AustraliaandOceania	Fiji	3.5.0
8490_6#45	GLOBAL	1996	ERR213263	AustraliaandOceania	Fiji	0.1.0
8490_6#46	GLOBAL	1996	ERR213264	AustraliaandOceania	Fiji	2.0.0
8490_6#47	GLOBAL	1996	ERR213265	AustraliaandOceania	Fiji	4.2.3
8490_6#48	GLOBAL	1996	ERR213266	AustraliaandOceania	Fiji	2.3.5
8490_6#49	GLOBAL	1996	ERR213267	AustraliaandOceania	Fiji	4.2.0
8490_6#50	GLOBAL	1996	ERR213268	AustraliaandOceania	Fiji	4.2.0
8490_6#51	GLOBAL	1995	ERR213269	AustraliaandOceania	Fiji	4.2.3
8490_6#52	GLOBAL	1995	ERR213270	AustraliaandOceania	Fiji	4.2.0
8490_6#53	GLOBAL	1995	ERR213271	AustraliaandOceania	Fiji	4.2.3
8490_6#54	GLOBAL	1995	ERR213272	AustraliaandOceania	Fiji	4.2.3
8490_6#55	GLOBAL	1995	ERR213273	AustraliaandOceania	Fiji	4.3.1
8490_6#56	GLOBAL	1994	ERR213274	AustraliaandOceania	Fiji	2.3.5
8490_6#57	GLOBAL	1994	ERR213275	AustraliaandOceania	Fiji	2.3.5
8490_6#58	GLOBAL	1994	ERR213276	AustraliaandOceania	Fiji	4.2.3
8490_6#59	GLOBAL	1994	ERR213277	AustraliaandOceania	Fiji	4.2.3
8490_6#60	GLOBAL	1994	ERR213278	AustraliaandOceania	Fiji	4.2.3
8490_6#61	GLOBAL	1994	ERR213279	AustraliaandOceania	Fiji	4.2.3
8490_6#62	GLOBAL	1994	ERR213280	AustraliaandOceania	Fiji	4.2.1
8490_6#63	GLOBAL	1994	ERR213281	AustraliaandOceania	Fiji	2.3.5
8490_6#64	GLOBAL	1994	ERR213282	AustraliaandOceania	Fiji	2.3.5
8490_6#65	GLOBAL	1994	ERR213283	AustraliaandOceania	Fiji	2.3.5
8490_6#66	GLOBAL	1994	ERR213284	AustraliaandOceania	Fiji	2.3.5
8490_6#67	GLOBAL	1994	ERR213285	AustraliaandOceania	Fiji	4.3.1
8490_6#68	GLOBAL	1994	ERR213286	AustraliaandOceania	Fiji	2.3.5

8490_6#69	GLOBAL	1996	ERR213287	AustraliaandOceania	Fiji	4.2.3
8490_6#70	GLOBAL	2008	ERR213288	AustraliaandOceania	Fiji	4.2.2
8490_6#71	GLOBAL	2008	ERR213289	AustraliaandOceania	Fiji	4.2.2
8490_6#72	GLOBAL	2008	ERR213290	AustraliaandOceania	Fiji	4.2.2
Salmonella_enterica_subsp_enterica _serovar_Typhi_str_UJ308A_v1	GLOBAL	2012	SalTypUJ308A 1.0	AustraliaandOceania	PapuaNewGuinea	#N/A
Salmonella_enterica_subsp_enterica _serovar_Typhi_str_UJ816A_v1	GLOBAL	2012	SalTypUJ816A 1.0	AustraliaandOceania	PapuaNewGuinea	#N/A
10349_1#84	GLOBAL	1916	ERR343332	Europe	Russia	#N/A
10425_1#13	GLOBAL	1996	ERR349343	Europe	Russia	4.1.0
10492_1#3	GLOBAL	2009	ERR352256	Europe	Malta	3.1.0
10592_2#53	GLOBAL	2009	ERR360501	Europe	France(mother-child,Africanname)	3.1.1
10592_2#81	GLOBAL	2009	ERR360529	Europe	France(mother-child,Africanname)	3.1.1
10593_2#32	GLOBAL	2009	ERR360645	Europe	France_Africanmeal	3.1.1
10593_2#74	GLOBAL	2009	ERR360687	Europe	France_Africanmeal	3.1.1
10349_1#73	GLOBAL	2011	ERR343321	N.America	Mexico	2.0.2
10592_2#50	GLOBAL	1998	ERR360498	N.America	Mexico	2.3.2
10593_2#2	GLOBAL	1972	ERR360615	N.America	Mexico	2.3.2
9472_4#78	GLOBAL	1958	ERR294858	N.America	USA	3.1.0
Salmonella_enterica_subsp_enterica _serovar_Typhi_str_E98_3139_v1	GLOBAL	1998	ASM18037v1	N.America	Mexico	#N/A
10349_1#60	GLOBAL	2010	ERR343308	S.America	SouthAmerica	2.3.2
10349_1#70	GLOBAL	2011	ERR343318	S.America	SouthAmerica	2.2.0
10492_1#77	GLOBAL	2012	ERR352330	S.America	ElSalvador	2.3.2
10541_1#57	GLOBAL	2001	ERR353330	S.America	Argentina	2.0.0
10541_1#58	GLOBAL	1988	ERR353331	S.America	Argentina	2.3.3
10541_1#60	GLOBAL	2004		S.America	Argentina	#N/A
10541_1#62	GLOBAL	1988	ERR353334	S.America	Argentina	4.1.0
10541_1#64	GLOBAL	2006	ERR353335	S.America	Argentina	2.3.3
10541_1#66	GLOBAL	1905	ERR353336	S.America	Argentina	2.3.3

10541_1#68	GLOBAL	1999	ERR353338	S.America	Argentina	2.0.0
10541_1#71	GLOBAL	1905	ERR353339	S.America	Argentina	4.1.0
10541_1#73	GLOBAL	2002	ERR353340	S.America	Argentina	2.3.2
10541_1#74	GLOBAL	1905	ERR353341	S.America	Argentina	4.1.0
10541_1#75	GLOBAL	1905	ERR353342	S.America	Argentina	2.3.2
10592_2#38	GLOBAL	1998	ERR360486	S.America	Peru	0.1.3
10593_2#37	GLOBAL	2000	ERR360650	S.America	Peru	2.3.3
10593_2#39	GLOBAL	2002	ERR360652	S.America	FrenchGuiana	2.5.0
10593_2#67	GLOBAL	2002	ERR360680	S.America	FrenchGuiana	2.5.0
10425_1#10	GLOBAL	1939	ERR349340	Unknown	Unknown	#N/A
10492_1#15	GLOBAL	2012	ERR352268	Unknown	Unknown	4.3.1
10492_1#23	GLOBAL	2011	ERR352276	Unknown	Unknown	4.3.1
10492_1#33	GLOBAL	2011	ERR352286	Unknown	Unknown	4.3.1
10492_1#39	GLOBAL	2011	ERR352292	Unknown	Unknown	3.5.4
10492_1#52	GLOBAL	2011	ERR352305	Unknown	Unknown	4.3.1
10492_1#84	GLOBAL	2011	ERR352337	Unknown	Unknown	4.1.0
10493_1#11	GLOBAL	2011	ERR352436	Unknown	Unknown	3.3.0
10493_1#22	GLOBAL	2011	ERR352447	Unknown	Unknown	4.3.1
10493_1#28	GLOBAL	2011	ERR352453	Unknown	Unknown	1.1.4
10493_1#49	GLOBAL	2011	ERR352474	Unknown	Unknown	4.3.1
10493_1#50	GLOBAL	2011	ERR352475	Unknown	Unknown	2.5.0
10493_1#63	GLOBAL	2011	ERR352488	Unknown	Unknown	3.5.3
10493_1#86	GLOBAL	2012	ERR352511	Unknown	Unknown	3.0.0
10541_2#10	GLOBAL	2011	ERR352943	Unknown	Unknown	4.3.1
10562_2#10	GLOBAL	2012	ERR357765	Unknown	Unknown	4.3.1
10562_2#17	GLOBAL	2011	ERR357772	Unknown	Unknown	3.3.0
10562_2#18	GLOBAL	2011	ERR357773	Unknown	Unknown	4.3.1
10562_2#35	GLOBAL	2011	ERR357790	Unknown	Unknown	2.2.2
11642_2#15	LONDON_TRAVELLERS	2010		Unknown	Unknown	4.3

11642_2#29	LONDON_TRAVELLERS	2010		Unknown	Unknown	3.3.1
11642_2#49	LONDON_TRAVELLERS	2010		Unknown	Unknown	4.3
11642_2#51	LONDON_TRAVELLERS	2010		Unknown	Unknown	4.3.1
11642_2#69	LONDON_TRAVELLERS	2011		Unknown	Unknown	4.3.1
11642_2#7	LONDON_TRAVELLERS	2009		Unknown	Unknown	4.3
11800_1#14	LONDON_TRAVELLERS	2005		Unknown	Unknown	3.1.1
11800_1#15	LONDON_TRAVELLERS	2005		Unknown	Unknown	4.3.1
11800_1#18	LONDON_TRAVELLERS	2005		Unknown	Unknown	4.3.1
11800_1#24	LONDON_TRAVELLERS	2006		Unknown	Unknown	3.0.1
11800_1#42	LONDON_TRAVELLERS	2006		Unknown	Unknown	2.0.2
11800_1#7	LONDON_TRAVELLERS	2005		Unknown	Unknown	4.3.1
11800_1#9	LONDON_TRAVELLERS	2005		Unknown	Unknown	4.3.1
12045_3#70	LONDON_TRAVELLERS	2005		Unknown	Unknown	4.3
12045_3#72	LONDON_TRAVELLERS	2005		Unknown	Unknown	4.3.1
12045_3#75	LONDON_TRAVELLERS	2006		Unknown	Unknown	4.3
12045_3#76	LONDON_TRAVELLERS	2006		Unknown	Unknown	4.3.1
12045_3#90	LONDON_TRAVELLERS	2009		Unknown	Unknown	unknown

9.3 All iNTS organisms analysed in Chapter 5

	All iNTS isolates from TSAP[2] & non-TSAP projects[3] in Ghana (N=166)							
iNTS isolates analyzed[1] (N=945)	Burkina Faso	Ghana[4]	Guinea-Bissau	Kenya	Madagascar	Senegal	South Africa	Tanzania
	12	133	9	1	4	2	1	4
	4 (Polesgo)	84 (Asante Akim North)	6 (Simao Hospital)	1 (Kibera)	3 (CHU Tsaralalana)	1 (IPS)		2 (Moshi Urban)
	8 (NiokoII)	49 (Agogo)[5]	2 (Bandim)		1 (Isotry)	1 (Dominique hospital)		1 (Moshi Rural)
		36 ("IsolateAgogo")	1 (Belem)					1 (Moshi Other)
		5 ("FISA")						
		3 ("TYSA")						
		5 (unidentified)						
	Published iNTS Typhimurium ST313 Lineage II isolates (N=102)[6]							
	DRC[7]	Kenya	Malawi	Mali	Mozambique	Nigeria	Uganda	
	8	9	55	18	3	6	3	
	Published iNTS Enteritidis ST11 isolates (N=677)[8]							
	Western Africa	Central & Eastern Africa	Southern Africa	Northern Africa	Rest of the World			
	90	262	131	11	183			

[1] Total 945 iNTS organisms were analysed in this manuscript: 166 iNTS isolates from the TSAP and other Ghana projects; sequenced and published 102 iNTS serovar typhimurium ST313 Lineage II isolates from seven countries (DRC/Kenya/Malawi/Mali/Mozambique/Nigeria/Uganda); and sequenced and published 594 (out of 677) iNTS serovar Enteritidis ST11 isolates (See Chapter 9 Appendices for the metadata).

[2] TSAP: Typhoid Fever Surveillance Program (Von Kalckreuth *et al.* 2016; Marks *et al.* 2017). Of the ten countries under the TSAP, no iNTS was found in Sudan and Ethiopia. 4 and 1 iNTS strains were identified from Madagascar and South Africa, respectively, through the whole genome sequencing; no iNTS isolates were reported from Madagascar and South Africa based on the blood culture result. Few analysed iNTS isolates, which may have been detected outside the strictly predefined surveillance catchment area, are considered for the bacterial genomic analysis, but excluded from the incidence estimation of the multidrug resistant iNTS in respective sites in Table 5.4. The 166 iNTS isolates included for the final genomic analyses are based on the screening of whole genome sequenced results.

[3] Non-TSAP projects in Ghana include the "Febrile Illnesses Surveillance in Africa (FISA)", "Typhoid Surveillance in Africa (TYSA)", and "IsolateAgogo" conducted in Agogo.

[4] Ghana: 133 iNTS isolates analysed in this manuscript include 84 iNTS detected through the TSAP in Asante Akim North and 49 iNTS from several non-TSAP projects conducted in Agogo.

[5] 49 (Agogo): 49 iNTS isolates detected from various non-TSAP projects in Agogo, Ghana as listed in this table.

[6] Total 102 iNTS Typhimurium ST313 Lineage II isolates, which had been collected in seven countries in sub-Saharan Africa and whole genome sequenced, were published and raw sequence data accessible at the Wellcome Trust Sanger Institute. Global collection of *S.* Typhimurium and additional *S.* Typhimurium from: Malawi, Kenya, Mozambique, Uganda, DRC, Nigeria, and Mali (Okoro *et al.* 2012); Nigeria and DRC (Leekitcharoenphon *et al.* 2013); Malawi (Feasey *et al.* 2014); Kenya (Kariuki *et al.* 2015b); Malawi (Msefula *et al.* 2012). Whole genome sequenced 166 iNTS isolates from TSAP and non-TSAP projects in Ghana listed in this table included 99 iNTS Typhimurium ST313 Lineage II . This 99 ST313 Lineage II was combined with the raw sequence data of 102 ST313 Lineage II published isolates listed in this footnote. Total 201 ST313 Lineage II isolates were further analysed.

[7] DRC: Democratic Republic of Congo

[8] Raw sequence data of the published global collection of 594/677 *S.* Enteritidis isolated from human and animal samples (Feasey *et al.* 2016) were accessible at the Wellcome Trust Sanger Institute. The associated metadata were publicly available online. These samples were collected and whole genome sequenced across the African continent and the world:

- Western Africa: Benin, Cameroon, Chad, Gabon, Guinea, Ivory Coast, Mali, Niger, and Senegal
- Central & Eastern Africa: Central African Republic, Comoros, Congo, Djibouti, Ethiopia, HPA, Kenya, Madagascar, Malawi, Mauritius, Mozambique, Rwanda, and Uganda
- Southern Africa: Republic of South Africa
- Northern Africa: Algeria, Egypt, Mauritania, Morocco, and Tunisia
- Rest of the World: Angola, Argentina, Columbia, Germany, Italy, Japan, PTG, Ratin-manufactured rat poison, Slovakia, Spain, Thailand, UK, Uruguay, USA, and unknown

9.3.1 Metadata of whole genome sequenced iNTS isolates from my data

Study_ID	Study_ID _verification	Lane_ID	Study_Source	Country	Site	Year	Sex	Age (Y)	Age (M)	ST	Serovars	gyrA_ mutation
83	BKF00083	21631_6#138	TSAP	BurkinaFaso	Nioko II	2012	Female	4	0	11	Enteritidis	WT
1141	BKF01141	21631_6#153	TSAP	BurkinaFaso	Polesgo	2013	Male	16	0	11	Enteritidis	WT
bkf01708	BKF01708	16404_4#84	TSAP	BurkinaFaso	Nioko II	2013	Male	30	0	11	Enteritidis	WT
bkf00121	BKF00121	16404_5#80	TSAP	BurkinaFaso	Polesgo	2012	Female	2	0	11	Enteritidis	WT
bkf00635	BKF00635	16549_7#2	TSAP	BurkinaFaso	Nioko II	2012	Female	7	0	10	Dublin	WT
bkf01713	BKF01713	16404_4#45	TSAP	BurkinaFaso	Nioko II	2013	Female	1	0	313	Typhimurium	WT
bkf00940	BKF00940	16404_4#49	TSAP	BurkinaFaso	Polesgo	2013	Female	3	0	313	Typhimurium	WT
bkf00392	BKF00392	16404_5#56	TSAP	BurkinaFaso	Nioko II	2012	Male	2	29	313	Typhimurium	WT
673	BKF00673	21631_6#145	TSAP	BurkinaFaso	Nioko II	2013	Female	9	0	313	Typhimurium	WT
707	BKF00707	21631_6#146	TSAP	BurkinaFaso	Nioko II	2013	Female	3	0	313	Typhimurium	WT
912	BKF00912	21631_6#147	TSAP	BurkinaFaso	Polesgo	2013	Male	1	0	313	Typhimurium	WT
57	BKF00057	21631_6#137	TSAP	BurkinaFaso	Nioko II	2012	Female	1	0	19	Typhimurium	WT
gha61020	61020	16549_8#55	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	11	Enteritidis	D87N
gha114606	114606	16404_5#31	TSAP	Ghana	Agogo	2011	Female	0	10	11	Enteritidis	WT
gha200805	200805	16404_5#54	TSAP	Ghana	Agogo	2011	Female	40	0	11	Enteritidis	WT
gha112732	112732	16549_7#61	TSAP	Ghana	Agogo	2010	Female	2	0	11	Enteritidis	D87N
gha60207	60207	16549_8#89	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	11	Enteritidis	D87G
gha113573	113573	16549_7#29	TSAP	Ghana	Agogo	2010	Female	2	0	11	Enteritidis	WT
gha113562	113562	16549_8#43	TSAP	Ghana	Agogo	2010	Female	3	0	11	Enteritidis	WT
gha114543	114543	16404_5#12	TSAP	Ghana	Agogo	2011	Female	3	0	11	Enteritidis	D87G
gha113480	113480	16549_7#67	TSAP	Ghana	Agogo	2010	Female	1	0	11	Enteritidis	D87G
gha114146	114146	16404_5#82	TSAP	Ghana	Agogo	2011	Male	1	0	11	Enteritidis	WT
gha113599	113599	16404_4#17	TSAP	Ghana	Agogo	2010	Male	2	0	11	Enteritidis	D87G

gha300240	300240	16404_4#74	TSAP	Ghana	Agogo	2010	Female	18	0	11	Enteritidis	D87G
115116	115116	21631_4#99	TSAP	Ghana	Agogo	2011	Male	2	0	11	Enteritidis	D87G
gha114062	114062	16549_8#13	TSAP	Ghana	Agogo	2011	Female	1	0	11	Enteritidis	D87N
500666	500666	21631_5#40	TSAP	Ghana	Agogo	2011	Female	36	0	11	Enteritidis	D87Y
114900	114900	21631_5#92	TSAP	Ghana	Agogo	2011	Female	1	0	11	Enteritidis	D87Y
113718	113718	21631_4#42	TSAP	Ghana	Agogo	2011	Male	3	0	11	Enteritidis	WT
gha113491	113491	16399_3#16	TSAP	Ghana	Agogo	2010	Female	0	8	11	Enteritidis	WT
gha601123	601123	16399_3#1	unknown	Ghana	Agogo	unknown	0	0	0	10	Dublin	WT
gha56474	56474	16399_4#62	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	10	Dublin	WT
115613	115613	21631_4#117	TSAP	Ghana	Agogo	2012	Male	1	0	10	Dublin	WT
gha112574	112574	16404_5#24	TSAP	Ghana	Agogo	2010	Female	0	8	10	Dublin	WT
gha114361	114361	16404_5#28	TSAP	Ghana	Agogo	2011	Female	3	0	10	Dublin	WT
gha114586	114586	16549_7#39	TSAP	Ghana	Agogo	2011	Female	2	0	10	Dublin	WT
114424	114424	21631_4#76	TSAP	Ghana	Agogo	2011	Female	0	10	10	Dublin	WT
114720	114720	21631_4#90	TSAP	Ghana	Agogo	2011	Male	1	0	10	Dublin	WT
114964	114964	21631_4#92	TSAP	Ghana	Agogo	2011	Female	3	0	10	Dublin	WT
115601	115601	21631_5#106	TSAP	Ghana	Agogo	2011	Female	1	0	10	Dublin	WT
200539	200539	21631_5#120	TSAP	Ghana	Agogo	2011	Female	42	0	10	Dublin	WT
gha114376	114376	16404_4#16	TSAP	Ghana	Agogo	2011	Female	1	0	10	Dublin	WT
gha115071	115071	16404_5#18	TSAP	Ghana	Agogo	2011	Female	2	0	10	Dublin	WT
gha114080	114080	16404_5#58	TSAP	Ghana	Agogo	2011	Female	3	0	10	Dublin	WT
gha300101	300101	16549_7#58	TSAP	Ghana	Agogo	2010	Female	51	0	10	Dublin	WT
gha115206	115206	16549_7#64	TSAP	Ghana	Agogo	2011	Female	1	0	10	Dublin	WT
gha114645	114645	16549_8#21	TSAP	Ghana	Agogo	2011	Female	1	0	10	Dublin	WT
gha113145	113145	16404_5#16	TSAP	Ghana	Agogo	2010	Male	3	0	313	Typhimurium	WT
gha113216	113216	16549_7#44	TSAP	Ghana	Agogo	2010	Female	1	0	313	Typhimurium	WT
gha500616	500616	16549_7#48	TSAP	Ghana	Agogo	2011	Female	15	0	313	Typhimurium	WT

gha113552	113552	16549_7#53	TSAP	Ghana	Agogo	2010	Female	3	0	313	Typhimurium	WT
gha109501	109501	16399_4#90	Tysa	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha109248	109248	16399_4#89	FISA	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha111979	111979	16399_4#91	FISA	Ghana	Agogo	2009	0	0	0	313	Typhimurium	WT
gha112057	112057	16404_4#27	FISA	Ghana	Agogo	2009	0	0	0	313	Typhimurium	WT
gha112108	112108	16404_4#29	FISA	Ghana	Agogo	2009	0	0	0	313	Typhimurium	WT
gha112006	112006	16404_4#34	FISA	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha54243	54243	16399_4#30	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha52718	52718	16399_3#19	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha65850	65850	16399_3#25	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha63245	63245	16399_3#42	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha56233	56233	16399_3#58	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha65681	65681	16399_3#59	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha65452	65452	16399_3#62	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha58774	58774	16399_3#65	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha61075	61075	16399_3#70	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha68741	68741	16399_3#72	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha55515	55515	16399_3#89	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha61549	61549	16399_4#18	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha61378	61378	16399_4#19	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha57488	57488	16399_4#20	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha68931	68931	16399_4#38	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha52308	52308	16399_4#57	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha54136	54136	16399_4#63	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha68182	68182	16399_4#7	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha61397	61397	16404_6#14	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha65358	65358	16404_6#17	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT

gha59341	59341	16404_6#19	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha61809	61809	16404_6#23	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha63275	63275	16404_6#32	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha59442	59442	16404_6#91	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha60767	60767	16549_8#64	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha60435	60435	16549_8#66	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha62721	62721	16549_8#68	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha62172	62172	16549_8#73	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha59920	59920	16549_8#75	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha54042	54042	16549_8#76	Isolate_Agogo	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha63979	63979	16549_8#81	Isolate_Agogo	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha116167	116167	16399_3#45	TSAP	Ghana	Agogo	2012	Female	1	0	313	Typhimurium	WT
gha113378	113378	16404_4#54	TSAP	Ghana	Agogo	2010	Male	2	0	313	Typhimurium	WT
gha113271	113271	16404_5#1	TSAP	Ghana	Agogo	2010	Male	0	8	313	Typhimurium	WT
gha300963	300963	16404_5#15	TSAP	Ghana	Agogo	2010	Female	69	0	313	Typhimurium	WT
gha113289	113289	16404_5#25	TSAP	Ghana	Agogo	2010	Male	3	0	313	Typhimurium	WT
gha116180	116180	16404_5#27	TSAP	Ghana	Agogo	2012	Female	3	0	313	Typhimurium	WT
gha500069	500069	16404_5#32	TSAP	Ghana	Agogo	2010	Female	28	0	313	Typhimurium	WT
gha116208	116208	16404_5#38	TSAP	Ghana	Agogo	2012	Female	0	8	313	Typhimurium	WT
gha113988	113988	16404_5#39	TSAP	Ghana	Agogo	2011	Female	1	0	313	Typhimurium	WT
gha113920	113920	16404_5#49	TSAP	Ghana	Agogo	2011	Female	0	7	313	Typhimurium	WT
gha113821	113821	16404_5#5	TSAP	Ghana	Agogo	2011	Female	0	10	313	Typhimurium	S83Y
gha114348	114348	16404_5#70	TSAP	Ghana	Agogo	2011	Female	9	0	313	Typhimurium	WT
gha300470	300470	16404_5#73	TSAP	Ghana	Agogo	2010	Female	40	0	313	Typhimurium	WT
gha113161	113161	16404_5#8	TSAP	Ghana	Agogo	2010	Female	1	0	313	Typhimurium	WT
gha116185	116185	16404_5#87	TSAP	Ghana	Agogo	2012	Male	0	6	313	Typhimurium	WT
gha112885	112885	16404_6#75	TSAP	Ghana	Agogo	2010	Female	10	0	313	Typhimurium	WT

gha500903	500903	16549_7#13	TSAP	Ghana	Agogo	2011	Female	35	0	313	Typhimurium	WT
gha113018	113018	16549_7#28	TSAP	Ghana	Agogo	2010	Female	3	0	313	Typhimurium	WT
gha115287	115287	16549_7#41	TSAP	Ghana	Agogo	2011	Female	1	0	313	Typhimurium	WT
gha115796	115796	16549_7#50	TSAP	Ghana	Agogo	2012	Female	0	11	313	Typhimurium	WT
gha113082	113082	16549_7#59	TSAP	Ghana	Agogo	2010	Female	2	0	313	Typhimurium	WT
gha112642	112642	16549_7#75	TSAP	Ghana	Agogo	2010	Female	1	0	313	Typhimurium	WT
gha113590	113590	16549_7#77	TSAP	Ghana	Agogo	2010	Female	3	0	313	Typhimurium	WT
gha113035	113035	16549_7#90	TSAP	Ghana	Agogo	2010	Female	2	0	313	Typhimurium	WT
gha200808	200808	16549_8#24	TSAP	Ghana	Agogo	2011	Female	51	0	313	Typhimurium	WT
115599	115599	21631_4#112	TSAP	Ghana	Agogo	2011	Female	4	0	313	Typhimurium	WT
115609-3	115609	21631_4#116	TSAP	Ghana	Agogo	2012	Female	5	0	313	Typhimurium	WT
115902	115902	21631_4#121	TSAP	Ghana	Agogo	2012	Female	1	0	313	Typhimurium	WT
116001	116001	21631_4#126	TSAP	Ghana	Agogo	2012	Male	7	0	313	Typhimurium	WT
116152	116152	21631_4#130	TSAP	Ghana	Agogo	2012	Male	0	3	313	Typhimurium	WT
116233	116233	21631_4#136	TSAP	Ghana	Agogo	2012	Female	1	0	313	Typhimurium	WT
116245	116245	21631_4#137	TSAP	Ghana	Agogo	2012	Female	1	0	313	Typhimurium	WT
200597	200597	21631_4#139	TSAP	Ghana	Agogo	2011	Female	60	0	313	Typhimurium	WT
300059-2	300059	21631_4#153	TSAP	Ghana	Agogo	2010	Female	61	0	313	Typhimurium	WT
113336-2	113336	21631_4#23	TSAP	Ghana	Agogo	2010	Female	0	0	313	Typhimurium	WT
113734	113734	21631_4#43	TSAP	Ghana	Agogo	2011	Female	1	0	313	Typhimurium	WT
114226-2	114226	21631_4#69	TSAP	Ghana	Agogo	2011	Male	0	0	313	Typhimurium	WT
114567	114567	21631_4#81	TSAP	Ghana	Agogo	2011	Female	1	0	313	Typhimurium	WT
115573	115573	21631_5#102	TSAP	Ghana	Agogo	2011	Male	5	0	313	Typhimurium	WT
115589-2	115589	21631_5#105	TSAP	Ghana	Agogo	2011	Female	11	0	313	Typhimurium	WT
115932-2	115932	21631_5#114	TSAP	Ghana	Agogo	2012	Female	1	0	313	Typhimurium	WT
300454	300454	21631_5#141	TSAP	Ghana	Agogo	2010	Female	48	0	313	Typhimurium	WT
112855	112855	21631_5#63	TSAP	Ghana	Agogo	2010	Female	3	0	313	Typhimurium	WT

113396	113396	21631_5#70	TSAP	Ghana	Agogo	2010	Female	0	11	313	Typhimurium	WT
113848	113848	21631_5#75	TSAP	Ghana	Agogo	2011	Female	1	0	313	Typhimurium	S83Y
300707	300707	21631_5#8	TSAP	Ghana	Agogo	2010	Female	53	0	313	Typhimurium	WT
114359-W	114359	21631_5#89	TSAP	Ghana	Agogo	2011	Female	0	0	313	Typhimurium	WT
gha103426	103426	16399_4#87	tysa	Ghana	Agogo	2007	0	0	0	313	Typhimurium	WT
gha108153	108153	16399_4#88	tysa	Ghana	Agogo	2008	0	0	0	313	Typhimurium	WT
gha79679	79679	16399_3#18	unknown	Ghana	unknown	unknown	0	0	0	359	Virchow	WT
gha75084	75084	16404_4#30	unknown	Ghana	unknown	unknown	0	0	0	183	Enteritidis	WT
gha300523	300523	16404_5#9	TSAP	Ghana	unknown	2010	Female	22	0	2107	Enteritidis	WT
gha97271	97271	16399_4#14	unknown	Ghana	unknown	unknown	0	0	0	321	Muenster	WT
gha66843	66843	16399_4#24	Isolate_Agogo	Ghana	unknown	2008	0	0	0	308	Poona	WT
gha62629	62629	16399_3#76	Isolate_Agogo	Ghana	unknown	2008	0	0	0	339	Stanleyville	WT
gha70948	70948	16399_3#6	unknown	Ghana	unknown	unknown	0	0	0	19	Typhimurium	WT
114575	114575	21631_4#83	TSAP	Ghana	unknown	2011	Male	0	11	19	Typhimurium	WT
gnb00128	00128	16404_4#36	TSAP	GuineaBissau	Bandim	2011	0	0	0	11	Enteritidis	WT
gnb00428	GNB00428	16404_4#72	TSAP	GuineaBissau	Simao Hospital	2010	Male	1	0	313	Typhimurium	WT
gnb00628	GNB00628	16404_4#79	TSAP	GuineaBissau	Bandim	2012	Female	1	0	313	Typhimurium	WT
gnb00526	GNB00526	16404_4#86	TSAP	GuineaBissau	Simao Hospital	2012	Female	3	0	145	Choleraesui	WT
gnb00217	GNB00217	16549_7#10	unknown	GuineaBissau	Simao Hospital	2010	Female	1	0	145	Choleraesui	WT
gnb00435	GNB00435	16549_7#9	unknown	GuineaBissau	Simao Hospital	2011	Female	1	0	145	Choleraesui	WT
gnb00588	00588	16404_4#43	TSAP	GuineaBissau	Simao Hospital	2012	Male	1	0	19	Typhimurium	WT
gnb01487	GNB01487	16549_7#19	TSAP	GuineaBissau	BELEM	2013	Male	0	0	19	Typhimurium	WT
86	GNB00086	21631_6#86	TSAP	GuineaBissau	Simao Hospital	2011	Female	5	0	19	Typhimurium	WT
2011731296	2011731296	16404_6#7	TSAP	Kenya	Kibera	2012	Male	55	0	313	Typhimurium	WT
1714	MGR01714	21631_6#38	TSAP	Madagascar	CHU Tsaralalana	2012	Male	0	18	11	Enteritidis	WT
1107	MGR01107	21631_6#32	TSAP	Madagascar	CHU Tsaralalana	2012	Male	0	8	11	Enteritidis	WT
1385	MGR01385	21631_6#34	TSAP	Madagascar	CHU Tsaralalana	2012	Male	1	0	11	Enteritidis	WT

mgr04250	MGR04250	16404_4#85	TSAP	Madagascar	Isotry	2013	Female	0	0	19	Typhimurium	WT
sen00489	SEN00489	16404_4#7	TSAP	Senegal	IPS	2012	Male	0	17	11	Enteritidis	WT
142	SEN00142	21631_6#58	TSAP	Senegal	Dominique hospital	2012	Male	66	0	19	Typhimurium	WT
rsa639626	639626	16404_4#55	TSAP	South Africa	unknown	unknown	0	0	0	11	Enteritidis	WT
tzn05677	FEVER5677M	16399_3#87	TSAP	Tanzania	Moshi Other	2011	Female	75	0	19	Typhimurium	WT
tzn06094	FEVER6094M	16399_4#12	TSAP	Tanzania	Moshi Rural	2012	Female	42	0	19	Typhimurium	WT
tzn05371	FEVER5371M	16399_4#5	TSAP	Tanzania	Moshi Urban	2013	Male	0	10	19	Typhimurium	WT
5738	FEVER5738M	21631_6#113	unknown	Tanzania	Moshi Urban	2011	Female	1	23	2533	unknown	WT

9.3.2 Metadata of whole genome sequenced *S.* Typhimurium ST313 lineage II isolates from my study and published data

My data: Source_IVI.

Published data: global collection of *S.* Typhimurium and additional *S.* Typhimurium from: Malawi, Kenya, Mozambique, Uganda, DRC, Nigeria, and Mali published by (Okoro *et al.* 2012); Nigeria and DRC data published by Leekitcharoenphon *et al.* (2013); Malawi data published by Feasey *et al.* (2014); Kenya data published by Kariuki *et al.* (2015b); Malawi data published by Msefula *et al.* (2012).

Lane_ID	LaneID_Country_StudySource_Year	Country	Source
16404_5#56	16404_5#56_BurkinaFaso_IVI_2012	Burkina Faso	IVI
16404_4#45	16404_4#45_BurkinaFaso_IVI_2013	Burkina Faso	IVI
16404_4#49	16404_4#49_BurkinaFaso_IVI_2013	Burkina Faso	IVI
21631_6#145	21631_6#145_BurkinaFaso_IVI_2013	Burkina Faso	IVI
21631_6#146	21631_6#146_BurkinaFaso_IVI_2013	Burkina Faso	IVI
21631_6#147	21631_6#147_BurkinaFaso_IVI_2013	Burkina Faso	IVI

16399_3#19	16399_3#19_Ghana_IVI_2007	Ghana	IVI
16399_3#58	16399_3#58_Ghana_IVI_2007	Ghana	IVI
16399_3#65	16399_3#65_Ghana_IVI_2007	Ghana	IVI
16399_3#70	16399_3#70_Ghana_IVI_2007	Ghana	IVI
16399_3#89	16399_3#89_Ghana_IVI_2007	Ghana	IVI
16399_4#20	16399_4#20_Ghana_IVI_2007	Ghana	IVI
16399_4#30	16399_4#30_Ghana_IVI_2007	Ghana	IVI
16399_4#57	16399_4#57_Ghana_IVI_2007	Ghana	IVI
16399_4#63	16399_4#63_Ghana_IVI_2007	Ghana	IVI
16399_4#87	16399_4#87_Ghana_IVI_2007	Ghana	IVI
16404_4#34	16404_4#34_Ghana_IVI_2007	Ghana	IVI
16404_6#19	16404_6#19_Ghana_IVI_2007	Ghana	IVI
16404_6#91	16404_6#91_Ghana_IVI_2007	Ghana	IVI
16549_8#66	16549_8#66_Ghana_IVI_2007	Ghana	IVI
16549_8#75	16549_8#75_Ghana_IVI_2007	Ghana	IVI
16549_8#76	16549_8#76_Ghana_IVI_2007	Ghana	IVI
16399_3#25	16399_3#25_Ghana_IVI_2008	Ghana	IVI
16399_3#42	16399_3#42_Ghana_IVI_2008	Ghana	IVI
16399_3#59	16399_3#59_Ghana_IVI_2008	Ghana	IVI
16399_3#62	16399_3#62_Ghana_IVI_2008	Ghana	IVI
16399_3#72	16399_3#72_Ghana_IVI_2008	Ghana	IVI
16399_4#18	16399_4#18_Ghana_IVI_2008	Ghana	IVI
16399_4#19	16399_4#19_Ghana_IVI_2008	Ghana	IVI
16399_4#38	16399_4#38_Ghana_IVI_2008	Ghana	IVI
16399_4#7	16399_4#7_Ghana_IVI_2008	Ghana	IVI
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16399_4#89	16399_4#89_Ghana_IVI_2008	Ghana	IVI

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16404_6#17	16404_6#17_Ghana_IVI_2008	Ghana	IVI
16404_6#23	16404_6#23_Ghana_IVI_2008	Ghana	IVI
16404_6#32	16404_6#32_Ghana_IVI_2008	Ghana	IVI
16549_8#64	16549_8#64_Ghana_IVI_2008	Ghana	IVI
16549_8#68	16549_8#68_Ghana_IVI_2008	Ghana	IVI
16549_8#73	16549_8#73_Ghana_IVI_2008	Ghana	IVI
16549_8#81	16549_8#81_Ghana_IVI_2008	Ghana	IVI
16399_4#91	16399_4#91_Ghana_IVI_2009	Ghana	IVI
16404_4#27	16404_4#27_Ghana_IVI_2009	Ghana	IVI
16404_4#29	16404_4#29_Ghana_IVI_2009	Ghana	IVI
16404_4#54	16404_4#54_Ghana_IVI_2010	Ghana	IVI
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16404_5#32	16404_5#32_Ghana_IVI_2010	Ghana	IVI
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16404_5#38	16404_5#38_Ghana_IVI_2012	Ghana	IVI

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21631_4#130	21631_4#130_Ghana_IVI_2012	Ghana	IVI
21631_4#136	21631_4#136_Ghana_IVI_2012	Ghana	IVI
21631_4#137	21631_4#137_Ghana_IVI_2012	Ghana	IVI
21631_5#114	21631_5#114_Ghana_IVI_2012	Ghana	IVI
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16404_4#79	16404_4#79_GuineaBissau_IVI_2012	Guinea-Bissau	IVI
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10868_5#3	10868_5#3_Kenya_2010	Kenya	published
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10868_5#6	10868_5#6_Kenya_2011	Kenya	published
10868_5#8	10868_5#8_Kenya_2011	Kenya	published
10900_4#64	10900_4#64_Kenya_2011	Kenya	published
10900_4#62	10900_4#62_Kenya_2012	Kenya	published
6470_8#8	6470_8#8_Malawi_2009	Malawi	published
6470_8#9	6470_8#9_Malawi_2009	Malawi	published
4821_1#2	4821_1#2_Malawi_2002	Malawi	published
4821_1#3	4821_1#3_Malawi_2002	Malawi	published
4821_1#4	4821_1#4_Malawi_2002	Malawi	published
4821_1#8	4821_1#8_Malawi_2002	Malawi	published

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4821_3#2	4821_3#2_Malawi_2002	Malawi	published
4821_1#11	4821_1#11_Malawi_2003	Malawi	published
4821_3#5	4821_3#5_Malawi_2003	Malawi	published
4821_2#1	4821_2#1_Malawi_2006	Malawi	published
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4949_5#3	4949_5#3_Malawi_2002	Malawi	published

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4238_8#6	4238_8#6_Malawi_2003	Malawi	published
4238_8#7	4238_8#7_Malawi_2003	Malawi	published
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4075_7#3	4075_7#3_Malawi_2004	Malawi	published
4075_7#4	4075_7#4_Malawi_2004	Malawi	published
4075_7#5	4075_7#5_Malawi_2004	Malawi	published
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4238_8#4	4238_8#4_Malawi_2004	Malawi	published
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4238_8#5	4238_8#5_Malawi_2005	Malawi	published
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4949_3#9	4949_3#9_Malawi_2005	Malawi	published
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3673_6	3673_6_Mali_2002	Mali	published
3673_7	3673_7_Mali_2002	Mali	published

4949_5#11	4949_5#11_Mali_2002	Mali	published
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4949_6#4	4949_6#4_Mali_2002	Mali	published
4949_6#5	4949_6#5_Mali_2002	Mali	published
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3901_3	3901_3_Mali_2005	Mali	published
4949_5#10	4949_5#10_Mali_2005	Mali	published
4949_5#6	4949_5#6_Mali_2005	Mali	published
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BL25_FQ312003	BL25_FQ312003_Nigeria_2004	Nigeria	published
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5116_5#8	5116_5#8_Nigeria_2010	Nigeria	published
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5116_7#2	5116_7#2_Uganda_2002	Uganda	published
02_03_002_FQ312003	02_03_002_FQ312003_DRC_2002	DRC	published
02_03_008_FQ312003	02_03_008_FQ312003_DRC_2002	DRC	published

05_102_FQ312003	05_102_FQ312003_DRC_2005	DRC	published
07_022_FQ312003	07_022_FQ312003_DRC_2007	DRC	published
5116_5#10	5116_5#10_DRC_1988	DRC	published
5116_6#9	5116_6#9_DRC_1991	DRC	published
5116_7#4	5116_7#4_DRC_1991	DRC	published
5116_6#8	5116_6#8_DRC_1992	DRC	published

9.3.3 Metadata of whole genome sequenced *S.* Enteritidis ST11 isolates from published data

Reproduced from Feasey *et al.* (2016): 677 *S.* Enteritidis ST11 isolates of which 594 isolates were analysed.

Sequencing Tag	Accession number	Strain name	Country of origin	Phage type	Date of isolation	Year of isolation
10071_5#1	ERS235824	482916	Republic of South Africa	Unknown	2010-11-09	2010
10071_5#10	ERS235833	332287	Republic of South Africa	Unknown	2009-09-18	2009
10071_5#11	ERS235834	250994	Republic of South Africa	Unknown	2006-05-02	2006
10071_5#13	ERS235836	616854	Republic of South Africa	Unknown	2012-06-13	2012
10071_5#14	ERS235837	584643	Republic of South Africa	Unknown	2012-04-25	2012
10071_5#15	ERS235838	503944	Republic of South Africa	Unknown	2011-09-07	2011
10071_5#16	ERS235839	454790	Republic of South Africa	Unknown	2006-03-30	2006
10071_5#17	ERS235840	285561	Republic of South Africa	Unknown	2009-05-19	2009
10071_5#18	ERS235841	283959	Republic of South Africa	Unknown	2009-03-21	2009
10071_5#19	ERS235842	238663	Republic of South Africa	Unknown	2008-02-27	2008
10071_5#2	ERS235825	361592	Republic of South Africa	Unknown	2010-06-24	2010
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10071_5#21	ERS235844	624887	Republic of South Africa	Unknown	2012-06-13	2012
10071_5#22	ERS235845	584640	Republic of South Africa	Unknown	2012-02-08	2012

10071_5#23	ERS235846	508751	Republic of South Africa	Unknown	2011-09-09	2011
10071_5#24	ERS235847	1029414	Republic of South Africa	Unknown	2010-06-18	2010
10071_5#25	ERS235848	380410	Republic of South Africa	Unknown	2010-06-26	2010
10071_5#26	ERS235849	258179	Republic of South Africa	Unknown	2008-09-04	2008
10071_5#27	ERS235850	180211	Republic of South Africa	Unknown	2008-01-06	2008
10071_5#28	ERS235851	247274	Republic of South Africa	Unknown	2008-05-14	2008
10071_5#29	ERS235852	631484	Republic of South Africa	Unknown	2012-08-14	2012
10071_5#3	ERS235826	283954	Republic of South Africa	Unknown	2009-03-16	2009
10071_5#30	ERS235853	570890	Republic of South Africa	Unknown	2012-01-08	2012
10071_5#31	ERS235854	684394	Republic of South Africa	Unknown	2011-09-30	2011
10071_5#32	ERS235855	172848	Republic of South Africa	Unknown	2007-12-23	2007
10071_5#33	ERS235856	481587	Republic of South Africa	Unknown	2010-11-09	2010
10071_5#34	ERS235857	245880	Republic of South Africa	Unknown	2008-02-20	2008
10071_5#35	ERS235858	468205	Republic of South Africa	Unknown	2010-10-19	2010
10071_5#36	ERS235859	236817	Republic of South Africa	Unknown	2008-01-07	2008
10071_5#37	ERS235860	626279	Republic of South Africa	Unknown	2012-08-16	2012
10071_5#38	ERS235861	492221	Republic of South Africa	Unknown	2011-04-27	2011
10071_5#39	ERS235862	684397	Republic of South Africa	Unknown	2008-04-09	2008
10071_5#4	ERS235827	603671	Republic of South Africa	Unknown	2012-06-05	2012
10071_5#40	ERS235863	468192	Republic of South Africa	Unknown	2010-09-02	2010
10071_5#41	ERS235864	119691	Republic of South Africa	Unknown	2007-01-03	2007
10071_5#42	ERS235865	283957	Republic of South Africa	Unknown	2009-03-16	2009
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10071_5#45	ERS235868	626285	Republic of South Africa	Unknown	2012-08-11	2012
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10071_5#50	ERS235873	254602	Republic of South Africa	Unknown	2008-09-02	2008
10071_5#51	ERS235874	358520	Republic of South Africa	Unknown	2006-05-04	2006
10071_5#52	ERS235875	533511	Republic of South Africa	Unknown	2011-11-08	2011
10071_5#53	ERS235876	570523	Republic of South Africa	Unknown	2012-01-08	2012
10071_5#54	ERS235877	261627	Republic of South Africa	Unknown	2008-09-02	2008
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10071_5#56	ERS235879	348823	Republic of South Africa	Unknown	2010-05-24	2010
10071_5#57	ERS235880	245891	Republic of South Africa	Unknown	2008-05-14	2008
10071_5#58	ERS235881	319189	Republic of South Africa	Unknown	2009-09-18	2009
10071_5#59	ERS235882	319184	Republic of South Africa	Unknown	2009-07-11	2009
10071_5#6	ERS235829	590212	Republic of South Africa	Unknown	2012-05-15	2012
10071_5#60	ERS235883	380425	Republic of South Africa	Unknown	2010-06-30	2010
10071_5#61	ERS235884	569257	Republic of South Africa	Unknown	2011-12-26	2011
10071_5#62	ERS235885	249309	Republic of South Africa	Unknown	2008-02-20	2008
10071_5#63	ERS235886	496155	Republic of South Africa	Unknown	2011-07-02	2011
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10071_5#67	ERS235890	250909	Republic of South Africa	Unknown	2008-09-04	2008
10071_5#7	ERS235830	503933	Republic of South Africa	Unknown	2011-07-02	2011
10071_5#8	ERS235831	358519	Republic of South Africa	Unknown	2010-05-30	2010
10071_5#9	ERS235832	332662	Republic of South Africa	Unknown	2009-10-01	2009
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10156_1#10	ERS235900	603668	Republic of South Africa	Unknown	2012-05-15	2012
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10156_1#12	ERS235902	511112	Republic of South Africa	Unknown	2011-09-07	2011
10156_1#13	ERS235903	250545	Republic of South Africa	Unknown	2006-05-02	2006
10156_1#14	ERS235904	115456	Republic of South Africa	Unknown	2006-11-17	2006
10156_1#15	ERS235905	360688	Republic of South Africa	Unknown	2010-04-28	2010
10156_1#16	ERS235906	177883	Republic of South Africa	Unknown	2007-12-23	2007
10156_1#17	ERS235907	575404	Republic of South Africa	Unknown	2006-03-30	2006
10156_1#18	ERS235908	596719	Republic of South Africa	Unknown	2012-05-15	2012
10156_1#19	ERS235909	516364	Republic of South Africa	Unknown	2011-10-13	2011
10156_1#2	ERS235892	547922	Republic of South Africa	Unknown	2011-12-26	2011
10156_1#20	ERS235910	272011	Republic of South Africa	Unknown	2009-01-20	2009
10156_1#21	ERS235911	249308	Republic of South Africa	Unknown	2008-05-13	2008
10156_1#22	ERS235912	201566	Republic of South Africa	Unknown	2008-01-06	2008
10156_1#23	ERS235913	469500	Republic of South Africa	Unknown	2010-10-19	2010
10156_1#24	ERS235914	1030047	Republic of South Africa	Unknown	2011-09-30	2011
10156_1#25	ERS235915	624885	Republic of South Africa	Unknown	2012-08-14	2012
10156_1#26	ERS235916	586365	Republic of South Africa	Unknown	2012-04-25	2012
10156_1#27	ERS235917	516360	Republic of South Africa	Unknown	2011-10-13	2011
10156_1#28	ERS235918	318064	Republic of South Africa	Unknown	2009-07-11	2009
10156_1#29	ERS235919	262647	Republic of South Africa	Unknown	2009-01-10	2009
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10156_1#32	ERS235922	171403	Republic of South Africa	Unknown	2007-12-07	2007
10156_1#33	ERS235923	236888	Republic of South Africa	Unknown	2008-02-21	2008
10156_1#34	ERS235924	249299	Republic of South Africa	Unknown	2008-05-13	2008
10156_1#35	ERS235925	348816	Republic of South Africa	Unknown	2010-05-24	2010
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10156_1#39	ERS235929	1025081	Republic of South Africa	Unknown	2008-11-12	2008
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10156_1#40	ERS235930	466244	Republic of South Africa	Unknown	2010-09-02	2010
10156_1#41	ERS235931	426007	Republic of South Africa	Unknown	2010-06-24	2010
10156_1#42	ERS235932	333519	Republic of South Africa	Unknown	2009-10-01	2009
10156_1#43	ERS235933	308821	Republic of South Africa	Unknown	2009-05-19	2009
10156_1#44	ERS235934	383167	Republic of South Africa	Unknown	2010-06-30	2010
10156_1#45	ERS235935	464793	Republic of South Africa	Unknown	2010-09-19	2010
10156_1#46	ERS235936	679982	Republic of South Africa	Unknown	2010-06-18	2010
10156_1#47	ERS235937	672637	Republic of South Africa	Unknown	2010-01-25	2010
10156_1#48	ERS235938	682773	Republic of South Africa	Unknown	2011-07-04	2011
10156_1#5	ERS235895	263174	Republic of South Africa	Unknown	2009-01-20	2009
10156_1#50	ERS235940	261629	Republic of South Africa	Unknown	2009-01-10	2009
10156_1#51	ERS235941	682965	Republic of South Africa	Unknown	2011-09-20	2011
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8987_8#4	ERS188191	A39959a	Malawi	Unknown	2006-02-19	2006
8987_8#40	ERS188227	A13216	Malawi	Unknown	2001-06-27	2001
8987_8#41	ERS188228	2702	Malawi	Unknown	1996-12-07	1996
8987_8#42	ERS188229	A7369	Malawi	Unknown	2000-01-14	2000
8987_8#45	ERS188232	A48460	Malawi	Unknown	2007-10-01	2007
8987_8#46	ERS188233	A59024	Malawi	Unknown	2010-06-07	2010
8987_8#47	ERS188234	A34057	Malawi	Unknown	2005-03-08	2005
8987_8#48	ERS188235	A46756	Malawi	Unknown	2007-05-15	2007
8987_8#49	ERS188236	A17698	Malawi	Unknown	2002-08-01	2002
8987_8#5	ERS188192	A28721	Malawi	Unknown	2004-04-05	2004
8987_8#50	ERS188237	A12756	Malawi	Unknown	2001-05-16	2001
8987_8#51	ERS188238	3857	Malawi	Unknown	1997-03-14	1997
8987_8#52	ERS188239	A9086	Malawi	Unknown	2000-06-19	2000
8987_8#54	ERS188241	A59040	Malawi	Unknown	2010-06-08	2010
8987_8#55	ERS188242	D43980	Malawi	Unknown	2007-10-09	2007
8987_8#56	ERS188243	A57601	Malawi	Unknown	2010-01-28	2010
8987_8#58	ERS188245	A30782	Malawi	Unknown	2004-08-26	2004
8987_8#59	ERS188246	D3558	Malawi	Unknown		1999
8987_8#6	ERS188193	A53601	Malawi	Unknown	2008-12-24	2008
8987_8#60	ERS188247	A12683	Malawi	Unknown	2001-05-11	2001
8987_8#61	ERS188248	6567	Malawi	Unknown	1997-12-01	1997
8987_8#63	ERS188250	A51583	Malawi	Unknown	2008-06-28	2008
8987_8#65	ERS188252	A54595	Malawi	Unknown	2009-03-30	2009
8987_8#66	ERS188253	A56756	Malawi	Unknown	2009-10-16	2009
8987_8#67	ERS188254	A53016	Malawi	Unknown	2008-10-22	2008

8987_8#68	ERS188255	A31243	Malawi	Unknown	2004-09-23	2004
8987_8#69	ERS188256	A9215	Malawi	Unknown	2000-07-07	2000
8987_8#70	ERS188257	D11119	Malawi	Unknown	2001-05-08	2000
8987_8#71	ERS188258	7909	Malawi	Unknown	1998-03-04	1998
8987_8#73	ERS188260	A54059	Malawi	Unknown	2009-02-04	2009
8987_8#74	ERS188261	D54684	Malawi	Unknown		2009
8987_8#75	ERS188262	A36950a	Malawi	Unknown	2005-09-02	2005
8987_8#76	ERS188263	A46277	Malawi	Unknown	2007-04-10	2007
8987_8#77	ERS188264	A31878	Malawi	Unknown	2004-11-01	2004
8987_8#78	ERS188265	D16245	Malawi	Unknown	2002-07-29	2002
8987_8#8	ERS188195	A40882	Malawi	Unknown	2006-04-14	2006
8987_8#80	ERS188267	9486	Malawi	Unknown		1998
8987_8#81	ERS188268	A51073	Malawi	Unknown	2008-05-10	2008
8987_8#84	ERS188271	A36678	Malawi	Unknown	2005-08-16	2005
8987_8#86	ERS188273	A53742	Malawi	Unknown	2009-01-07	2009
8987_8#88	ERS188275	D17739	Malawi	Unknown	2002-12-05	2002
8987_8#89	ERS188276	A7828	Malawi	Unknown	2000-02-21	2000
8987_8#9	ERS188196	A34142	Malawi	Unknown	2005-03-11	2005
8987_8#90	ERS188277	A53843	Malawi	Unknown	2009-01-18	2009
8987_8#91	ERS188278	A36950	Malawi	Unknown	2005-09-02	2005
8987_8#92	ERS188279	A45427	Malawi	Unknown	2007-02-15	2007
8987_8#93	ERS188280	A35261	Malawi	Unknown	2005-05-14	2005
8987_8#94	ERS188281	A41750	Malawi	Unknown	2006-06-13	2006
8987_8#95	ERS188282	1971	Malawi	Unknown	1996-09-24	1996
8987_8#96	ERS188283	D5408	Malawi	Unknown	2000-02-28	2000
9032_4#1	ERS188380	31353	Congo	Unknown	2010-11-05	2010
9032_4#10	ERS188389	33013	Congo	Unknown	2010-01-17	2011

9032_4#11	ERS188390	33033	Congo	Unknown	2011-01-19	2011
9032_4#12	ERS188391	33078	Congo	Unknown	2011-01-18	2011
9032_4#13	ERS188392	33393	Congo	Unknown	2011-01-29	2011
9032_4#14	ERS188393	33453	Congo	Unknown	2011-01-31	2011
9032_4#15	ERS188394	33513	Congo	Unknown	2011-02-02	2011
9032_4#16	ERS188395	33523	Congo	Unknown	2011-02-02	2011
9032_4#17	ERS188396	33623	Congo	Unknown	2011-02-03	2011
9032_4#18	ERS188397	33653	Congo	Unknown	2011-02-04	2011
9032_4#19	ERS188398	33663	Congo	Unknown	2011-02-04	2011
9032_4#2	ERS188381	32363	Congo	Unknown	2010-12-21	2010
9032_4#20	ERS188399	33673	Congo	Unknown	2011-02-05	2011
9032_4#21	ERS188400	33683	Congo	Unknown	2011-02-06	2011
9032_4#22	ERS188401	33693	Congo	Unknown	2011-02-07	2011
9032_4#23	ERS188402	33703	Congo	Unknown	2011-02-08	2011
9032_4#24	ERS188403	33713	Congo	Unknown	2011-02-08	2011
9032_4#25	ERS188404	33873	Congo	Unknown	2011-02-12	2011
9032_4#26	ERS188405	33893	Congo	Unknown	2011-02-13	2011
9032_4#27	ERS188406	33913	Congo	Unknown	2011-02-14	2011
9032_4#28	ERS188407	33923	Congo	Unknown	2011-02-14	2011
9032_4#29	ERS188408	33943	Congo	Unknown	2011-02-14	2011
9032_4#3	ERS188382	32013	Congo	Unknown	2010-12-06	2010
9032_4#30	ERS188409	33993	Congo	Unknown	2011-02-15	2011
9032_4#31	ERS188410	34083	Congo	Unknown	2011-02-19	2011
9032_4#32	ERS188411	34173	Congo	Unknown	2011-02-24	2011
9032_4#33	ERS188412	34193	Congo	Unknown	2011-02-24	2011
9032_4#34	ERS188413	34223	Congo	Unknown	2011-02-25	2011
9032_4#35	ERS188414	34233	Congo	Unknown	2011-02-25	2011

9032_4#36	ERS188415	34243	Congo	Unknown	2011-02-25	2011
9032_4#37	ERS188416	34253	Congo	Unknown	2011-02-25	2011
9032_4#38	ERS188417	34393	Congo	Unknown	2011-03-01	2011
9032_4#39	ERS188418	34403	Congo	Unknown	2011-03-01	2011
9032_4#4	ERS188383	32963	Congo	Unknown	2011-01-15	2011
9032_4#40	ERS188419	34413	Congo	Unknown	2011-03-02	2011
9032_4#41	ERS188420	34423	Congo	Unknown	2011-03-03	2011
9032_4#42	ERS188421	34443	Congo	Unknown	2011-03-03	2011
9032_4#44	ERS188423	34483	Congo	Unknown	2011-03-03	2011
9032_4#45	ERS188424	34493	Congo	Unknown	2011-03-04	2011
9032_4#46	ERS188425	34503	Congo	Unknown	2011-03-06	2011
9032_4#47	ERS188426	34563	Congo	Unknown	2011-03-07	2011
9032_4#48	ERS188427	34683	Congo	Unknown	2011-03-09	2011
9032_4#49	ERS188428	34853	Congo	Unknown	2011-03-15	2011
9032_4#5	ERS188384	32523	Congo	Unknown	2010-12-30	2010
9032_4#50	ERS188429	34863	Congo	Unknown	2011-03-15	2011
9032_4#51	ERS188430	34873	Congo	Unknown	2011-03-16	2011
9032_4#52	ERS188431	34893	Congo	Unknown	2011-03-16	2011
9032_4#53	ERS188432	34933	Congo	Unknown	2011-03-18	2011
9032_4#55	ERS188434	35203	Congo	Unknown	2011-03-27	2011
9032_4#56	ERS188435	35213	Congo	Unknown	2011-03-27	2011
9032_4#57	ERS188436	35223	Congo	Unknown	2011-03-28	2011
9032_4#58	ERS188437	35263	Congo	Unknown	2011-03-31	2011
9032_4#59	ERS188438	35433	Congo	Unknown	2011-04-02	2011
9032_4#6	ERS188385	32633	Congo	Unknown	2011-01-02	2011
9032_4#60	ERS188439	35443	Congo	Unknown	2011-04-02	2011
9032_4#61	ERS188440	35473	Congo	Unknown	2011-04-04	2011

9032_4#62	ERS188441	35563	Congo	Unknown	2011-04-05	2011
9032_4#63	ERS188442	36803	Congo	Unknown	2011-05-21	2011
9032_4#64	ERS188443	36723	Congo	Unknown	2011-05-16	2011
9032_4#65	ERS188444	36343	Congo	Unknown	2011-04-27	2011
9032_4#66	ERS188445	36313	Congo	Unknown	2011-04-27	2011
9032_4#67	ERS188446	36183	Congo	Unknown	2011-04-24	2011
9032_4#68	ERS188447	36173	Congo	Unknown	2011-04-22	2011
9032_4#69	ERS188448	36163	Congo	Unknown	2011-04-22	2011
9032_4#70	ERS188449	36103	Congo	Unknown	2011-04-20	2011
9032_4#71	ERS188450	35693	Congo	Unknown	2011-04-10	2011
9032_4#72	ERS188451	35773	Congo	Unknown	2011-04-18	2011
9032_4#73	ERS188452	35723	Congo	Unknown	2011-04-12	2011
9032_4#74	ERS188453	35713	Congo	Unknown	2011-04-10	2011
9032_4#8	ERS188387	32863	Congo	Unknown	2011-01-12	2011
9032_4#9	ERS188388	32853	Congo	Unknown	2010-11-28	2010
9032_4#92	ERS188471	1020983	Malawi	Unknown	2011-09-30	2011
9032_4#96	ERS188475	A59130	Malawi	Unknown	2010-06-20	2010
9716_8#10	ERS217265	119_2012K_187	USA	Unknown		2012
9716_8#11	ERS217266	120_2021	USA	Unknown		
9716_8#12	ERS217267	121_67	USA	Unknown		
9716_8#13	ERS217268	122_68	USA	Unknown		
9716_8#15	ERS217270	124_2711	USA	Unknown		
9716_8#16	ERS217271	125_81_2625	USA	Unknown		1981
9716_8#17	ERS217272	126_88_303	USA	Unknown		1988
9716_8#18	ERS217273	127_85_98	USA	Unknown		1985
9716_8#2	ERS217257	111_2012K_181	USA	Unknown		2011
9716_8#20	ERS217275	129_88_415	USA	Unknown		

9716_8#21	ERS217276	130_88_408	USA	Unknown		
9716_8#23	ERS217278	132_88_406	USA	Unknown		
9716_8#24	ERS217279	133_48_0565	USA	Unknown		1948
9716_8#25	ERS217280	135_50_3079	USA	Unknown		1949
9716_8#26	ERS217281	136_50_4630	USA	Unknown		1950
9716_8#27	ERS217282	137_50_5306	USA	Unknown		1950
9716_8#28	ERS217283	138_50_5646	Japan	Unknown		1950
9716_8#29	ERS217379	SAEN4	Congo	Unknown	Unknown	1988
9716_8#3	ERS217258	112_2012K_180	USA	Unknown		2012
9716_8#30	ERS217380	SAEN8	Congo	Unknown	Unknown	1988
9716_8#31	ERS217381	SAEN13	Congo	Unknown	Unknown	1988
9716_8#32	ERS217382	SAEN19	Congo	Unknown	Unknown	1989
9716_8#33	ERS217383	SAEN26	Congo	Unknown	Unknown	1989
9716_8#34	ERS217384	SAEN27	Congo	Unknown	Unknown	1989
9716_8#35	ERS217385	SAEN62	Congo	Unknown	Unknown	1989
9716_8#36	ERS217386	SAEN84	Congo	Unknown	Unknown	1989
9716_8#37	ERS217387	SAEN87	Congo	Unknown	Unknown	1989
9716_8#38	ERS217388	SAEN111	Congo	Unknown	Unknown	1990
9716_8#39	ERS217389	SAEN128	Congo	Unknown	Unknown	1990
9716_8#4	ERS217259	113_2012K_220	USA	Unknown		2012
9716_8#40	ERS217391	SAEN146	Congo	Unknown	Unknown	1990
9716_8#41	ERS217392	SAEN152	Congo	Unknown	Unknown	1990
9716_8#42	ERS217393	SAEN180	Congo	Unknown	Unknown	1990
9716_8#43	ERS217395	SAEN199	Congo	Unknown	Unknown	1991
9716_8#44	ERS217396	SAEN203	Congo	Unknown	Unknown	1991
9716_8#45	ERS217398	SAEN220	Congo	Unknown	Unknown	1991
9716_8#46	ERS217399	SAEN256	Congo	Unknown	Unknown	1991

9716_8#47	ERS217401	SAEN280	Congo	Unknown	Unknown	1991
9716_8#48	ERS217402	SAEN284	Congo	Unknown	Unknown	1991
9716_8#49	ERS217406	SAEN378	Congo	Unknown	Unknown	1992
9716_8#5	ERS217260	114_2012K_174	USA	Unknown		2012
9716_8#50	ERS217407	SAEN390	Congo	Unknown	Unknown	1992
9716_8#51	ERS217408	SAEN392	Congo	Unknown	Unknown	1992
9716_8#52	ERS217410	SAEN437	Congo	Unknown	Unknown	1992
9716_8#53	ERS217411	SAEN1975	Uganda	Unknown		1996
9716_8#54	ERS217413	SAEN2209	Uganda	Unknown		1996
9716_8#55	ERS217415	SAEN2862	Uganda	Unknown		1997
9716_8#56	ERS217418	SAEN4582	Uganda	Unknown		1997
9716_8#57	ERS217419	SAEN6442	Uganda	Unknown		1998
9716_8#58	ERS217420	SAEN6474	Uganda	Unknown		1998
9716_8#6	ERS217261	115_2012K_175	USA	Unknown		2012
9716_8#8	ERS217263	117_2012K_185	USA	Unknown		2012
9716_8#9	ERS217264	118_2012K_186	USA	Unknown		2012
9803_3#1	ERS217197	P2	Unknown	5	Unknown	2007
9803_3#10	ERS217206	P12	Unknown	6	Unknown	2007
9803_3#11	ERS217207	P13	Unknown	6	Unknown	2007
9803_3#12	ERS217208	P14	Unknown	1	Unknown	2007
9803_3#13	ERS217209	P15	Unknown	1	Unknown	2007
9803_3#14	ERS217210	P16	Unknown	1	Unknown	2007
9803_3#15	ERS217211	P17	Unknown	2	Unknown	2007
9803_3#16	ERS217212	P19	Unknown	2	Unknown	2007
9803_3#17	ERS217213	RD2	UK	Unknown	Unknown	2005
9803_3#18	ERS217214	RD3	UK	24	Unknown	2005
9803_3#19	ERS217215	RD6	UK	24	Unknown	2005

9803_3#2	ERS217198	P4	Unknown	5	Unknown	2007
9803_3#20	ERS217216	RD26	UK	35	Unknown	2005
9803_3#21	ERS217217	RD30	UK	6	Unknown	2005
9803_3#22	ERS217218	RD36	UK	7	Unknown	2005
9803_3#23	ERS217219	RD40	UK	Unknown	Unknown	2005
9803_3#24	ERS217220	RD42	UK	29	Unknown	2005
9803_3#25	ERS217221	RD44	UK	29	Unknown	2005
9803_3#26	ERS217222	RD46	UK	36	Unknown	2005
9803_3#27	ERS217223	RD45	UK	24	Unknown	2005
9803_3#29	ERS217225	RD50	UK	6	Unknown	2005
9803_3#3	ERS217199	P5	PTG	3	Unknown	2007
9803_3#30	ERS217226	RD51	UK	7	Unknown	2005
9803_3#31	ERS217227	RD54	UK	7	Unknown	2005
9803_3#32	ERS217228	RD55	UK	Unknown	Unknown	2005
9803_3#33	ERS217229	RD57	UK	7	Unknown	2005
9803_3#34	ERS217230	RD72	UK	4	Unknown	2005
9803_3#35	ERS217231	RD76	UK	4	Unknown	2005
9803_3#36	ERS217232	RD79	UK	35	Unknown	2005
9803_3#37	ERS217233	RD84	UK	45	Unknown	2005
9803_3#39	ERS217235	SEA	USA	13a	Unknown	1994
9803_3#4	ERS217200	P6	Unknown	3	Unknown	2007
9803_3#40	ERS217236	SEC	USA	13a	Unknown	1994
9803_3#41	ERS217237	SED	USA	13a	Unknown	1994
9803_3#42	ERS217238	EX4_PT21b	PTG	21b	Unknown	1996
9803_3#43	ERS217239	9508_195	USA	23	Unknown	1994
9803_3#44	ERS217240	9508_211	USA	23	Unknown	1994
9803_3#45	ERS217241	S4726_04	UK	14b	Unknown	2006

9803_3#46	ERS217242	S1750_06	PTG	1	Unknown	2006
9803_3#47	ERS217243	S6669_03L	PTG	1	Unknown	2006
9803_3#48	ERS217244	S6669_03N	PTG	1	Unknown	2006
9803_3#5	ERS217201	P7	Unknown	58	Unknown	2007
9803_3#50	ERS217246	99_CDC_H9556	USA	Unknown		
9803_3#51	ERS217247	100_8_403	USA	Unknown		2008
9803_3#53	ERS217249	102_AM36958_B	USA	Unknown		2008
9803_3#54	ERS217250	103_08_639	USA	Unknown		2008
9803_3#55	ERS217251	104_AM25928_B	USA	Unknown		2006
9803_3#56	ERS217252	105_2011K_1654	USA	Unknown		2011
9803_3#57	ERS217253	106_2011K_1681	USA	Unknown		2011
9803_3#58	ERS217254	107_2012K_147	USA	Unknown		2005
9803_3#59	ERS217255	108_2012K_179	USA	Unknown		2006
9803_3#6	ERS217202	P8	Unknown	Unknown	Unknown	2007
9803_3#7	ERS217203	P9	Spain	Unknown	Unknown	2007
9803_3#8	ERS217204	P10	Spain	Unknown	Unknown	2007
9803_3#9	ERS217205	P11	Spain	Unknown	Unknown	2007
JG009	SRP078456	C49	Columbia	Unknown		2008
JG0013	SRP078456	C75	Columbia	Unknown		2011
JG0014	SRP078456	C76	Columbia	Unknown		2011
SQ0025	168744	04-0307	USA	Unknown		2004
SQ0045	168743	98-0467	USA	Unknown		1998
SQ0013	168732	2010K-0300	Thailand	Unknown		2008
SQ0052	168763	SD380	USA	Unknown		2008
SQ0019	168738	2010K-2029	USA	Unknown		2010
SQ0053	168764	55795	USA	Unknown		2001
SQ0039	168756	2010K-1369	USA	Unknown		2010

SQ0007	168726	2010K-0267	Thailand	Unknown		2008
SQ0221	168795	J0915	USA	Unknown		2001
SQ0054	168765	SD277	USA	Unknown		2008
SQ0044	168844	96-0186	USA	Unknown		1996
SQ0004	168723	2009K-1651	USA	Unknown		2009
SQ0048	168845	CDC-STK -1280	Slovakia	Unknown		1965
SQ0057	168768	98961	USA	Unknown		2010
SQ0058	168769	61979	USA	Unknown		2002
SQ0030	168748	2010K-0263	Thailand	Unknown		2008
SQ0059	168770	61080	USA	Unknown		2002
SQ0041	168758	2010K-1832	USA	Unknown		2010
SQ0060	168771	34986	USA	Unknown		1998
SQ0011	168730	2010K-0287	Thailand	Unknown		2008
SQ0022	168741	84-1226	USA	Unknown		1984
SQ0035	168753	2010K-0345	Mauritius	Unknown		0
SQ0037	168843	2010K-0860	USA	Unknown		2010
SQ0055	168766	78296	USA	Unknown		2005
SQ0012	168731	2010K-0297	Thailand	Unknown		2008
SQ0177	168791	39997	USA	Unknown		1999
SQ0032	168750	2010K-0268	Thailand	Unknown		2008
SQ0015	168734	2010K-0303	Thailand	Unknown		2008
SQ0003	168722	2009K-0958	USA	Unknown		2009
SQ0024	168743	98-0467	USA	Unknown		1998
SQ0016	168735	2010K-0313	Mauritius	Unknown		0
SQ0178	168792	82631	USA	Unknown		2006
SQ0005	168724	2009K-1726	USA	Unknown		2009
SQ0017	168736	2010K-0329	Mauritius	Unknown		0

SQ0028	168746	2009K-0479	Uganda	Unknown		
SQ0006	168725	2010K-0262	Thailand	Unknown		2008
SQ0036	168754	2010K-0351	Mauritius	Unknown		0
SQ0033	168751	2010K-0277	Thailand	Unknown		2008
SQ0018	168737	2010K-1923	USA	Unknown		2010
SQ0056	168767	85366	USA	Unknown		2006
SQ0246	168940	UC06	USA	Unknown		2004
SQ0185	168942	MB04708	USA	Unknown		2002
SQ0009	168728	2010K-0284	Thailand	Unknown		2008
SQ0203	168678	CO52846	USA	Unknown		2004
SQ0046	168761	J0828	USA	Unknown		2001
SQ0238	168784	9810102B	USA	Unknown		1998
SQ0228	168774	gerald_D0M12ACXX_1_AAGCGA	USA	Unknown		1993
SQ0227	168773	gerald_D0M12ACXX_1_AAGGAC	USA	Unknown		1993
Salmonella_enterica_ subsp_enterica_serovar_ Enteritidis_str_P125109_v1	AM933172	P125109	UK	4		

9.4 All NTS organisms analysed in Chapter 6

9.4.1 Stool specimens collected

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Study Sites	Households	Individuals (Stool specimen collected & cultured)	Stool culture positive for nontyphoidal *Salmonella* (NTS)
Bissau, Guinea-Bissau	164	1077	26
Dakar, Senegal	211	1359	14
Total	375	2436	40

9.4.2 Metadata of whole genome sequenced NTS isolates

40 NTS isolates sequenced of which 37 were analysed.

Sample_ID	Sanger_ID	Lane_ID	Visit Date	Age (yr)	Sex (1=male; 2=female)	Isolate	Year	Senegal: GPS coordinates (LONGI) Guinea-Bissau (GB): Endereco residencial (tabz+casa)	Senegal: GPS coordinates (LATID) Guinea-Bissau: cidade/Municipio	Country	ST	Serovar
G0017	13958244	16399_4#44	06/05/2012	38	2	Salmonella	2012	11/70	BISSAU	GB	3475	
G0017	13958246	16399_4#60	06/05/2012	38	2	Salmonella	2012	11/70	BISSAU	GB	3475	
G0032	13958163	16399_3#77	06/07/2012	8	1	Salmonella	2012	11/108	BISSAU	GB	3703	
G0032	13958221	16399_4#50	06/07/2012	8	1	Salmonella	2012	11/108	BISSAU	GB	3703	
G0033	13958203	16399_4#1	06/07/2012	10	1	Salmonella	2012	11/108	BISSAU	GB	2126	
G0033	13958257	16399_4#53	06/07/2012	10	1	Salmonella	2012	11/108	BISSAU	GB	2126	
G0034	13958196	16399_3#56	06/07/2012	5	2	Salmonella	2012	11/108	BISSAU	GB	2126	
G0034	13958204	16399_4#9	06/07/2012	5	2	Salmonella	2012	11/108	BISSAU	GB	2126	
G0042	13958254	16399_4#29	06/08/2012	14	1	Salmonella	2012	11/80	BISSAU	GB	516	

G0267	13958212	16399_4#73	07/27/2012	1	2	Salmonella	2012	94/48	BISSAU	GB	3032	
G0454	13958187	16399_3#79	09/03/2012	40	2	Salmonella	2012	74/60	BISSAU	GB	NF*	
G0509	13958247	16399_4#68	09/11/2012	0	1	Salmonella	2012	74/35	BISSAU	GB	755	
G0560	13958294	16399_4#64	09/19/2012	13	2	Salmonella	2012	75/158	BISSAU	GB	3474	
G0575	13958283	16399_4#71	09/21/2012	15	2	Salmonella	2012	75/171	BISSAU	GB	3474	
G0893	13958215	16399_4#2	03/13/2013	15	1	Salmonella	2013	28/32	BISSAU	GB	3702	
G0894	13958185	16399_3#63	03/13/2013	12	1	Salmonella	2013	28/32	BISSAU	GB	3702	
G0896	13958295	16399_4#72	03/13/2013	6	2	Salmonella	2013	28/32	BISSAU	GB	3702	
G0907	13958292	16399_4#48	03/15/2013	32	1	Salmonella	2013	26/70	BISSAU	GB	516	
G0908	13958124	16399_3#50	03/15/2013	28	2	Salmonella	2013	26/70	BISSAU	GB	3468*	
G0912	13958164	16399_3#85	03/15/2013	22	2	Salmonella	2013	26/70	BISSAU	GB	516	
G0913	13958281	16399_4#55	03/15/2013	21	1	Salmonella	2013	26/70	BISSAU	GB	516	
G0915	13958149	16399_3#60	03/18/2013	35	2	Salmonella	2013	26/72	BISSAU	GB	3468	
G0916	13958284	16399_4#79	03/18/2013	31	2	Salmonella	2013	26/72	BISSAU	GB	516	
G0918	13958211	16399_4#65	03/18/2013	7	1	Salmonella	2013	26/72	BISSAU	GB	516	
G0919	13958147	16399_3#44	03/18/2013	0	2	Salmonella	2013	26/72	BISSAU	GB	3468	
G0921	13958252	16399_4#13	03/18/2013	30	2	Salmonella	2013	26/97	BISSAU	GB	516	
G0923	13958135	16399_3#43	03/18/2013	6	2	Salmonella	2013	26/97	BISSAU	GB	3468	
DJ1149_2	13958176	16399_3#86	09/27/2013	7	1	Salmonella	2013	14.45.954'N	17.23.587'W	Senegal	515	
DJ19646_8	13958256	16399_4#45	12/06/2013	17	1	Salmonella	2013	14.46.210'N	17.22.465'W	Senegal	1954	
DJ893_2	13958243	16399_4#36	10/01/2013	18	2	Salmonella	2013	14.46.161'N	17.23.616'W	Senegal	515	
DJ9240_9	13958227	16399_4#3	11/19/2013	7	1	Salmonella	2013	14.45.882'N	17.22.379'W	Senegal	33	
PE4278_5	13958160	16399_3#53	06/05/2013	6	1	Salmonella	2013	14.45.662'N	17.23.281'W	Senegal	1954	
PE589_5	13958223	16399_4#66	05/30/2013	15	2	Salmonella	2013	14.45.502'N	17.23.262'W	Senegal	516	
PE595_1	13958115	16399_3#73	05/27/2013	48	2	Salmonella	2013	14.45.516'N	17.23.436'W	Senegal	3470	
PN4129_13	13958234	16399_4#59	12/13/2013	2	2	Salmonella	2013	14.45.469'N	17.22.866'W	Senegal	1357	Corvallis
PN4129_17	13958239	16399_4#4	12/13/2013	20	1	Salmonella	2013	14.45.469'N	17.22.866'W	Senegal	1357	Corvallis
PN4129_3	13958152	16399_3#84	12/13/2013	19	2	Salmonella	2013	14.45.469'N	17.22.866'W	Senegal	1357	Corvallis
PW1547_3	13958291	16399_4#40	04/30/2013	29	2	Salmonella	2013	14.45.010'N	17.23.692'W	Senegal	11	Enteritidis
PW3498_6	13958182	16399_3#39	03/06/2013	3	2	Salmonella	2013	14.45.279'N	17.24.129'W	Senegal	13	
PW3512_11	13958200	16399_3#88	03/11/2013	59	2	Salmonella	2013	14.45.300'N	17.24.110'W	Senegal	308	Poona

9.5 Publications during DPhil candidature

First authored manuscripts (attached):

1. **Park S. E.**, Pham D. T., Boinett C., Wong V. K., Pak G. D., Panzer U. *et al*. The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa. *Nature Commun.* 9, 5094 (2018).

2. **Park S. E.**, Pak G. D., Aaby P., Adu-Sarkodie Y., Ali M. *et al*. The Relationship Between Invasive Nontyphoidal *Salmonella* Disease, Other Bloodstream Infections, and Malaria in Sub-Saharan Africa. *Clin Infect Dis.* 62 Suppl 1: S23-31 (2016).

3. **Park S. E.**, Toy T., Cruz Espinoza L. M., Panzner U., Mogeni O. D. *et al*. The Severe Typhoid in Africa program protocol: assessing the burden, severity, host immunity and carriage associated with invasive salmonellosis using prospective sentinel-based passive surveillance, healthcare utilization surveys, and prospective case-controlled and cohort study designs (Short Title: The SETA study protocol). (Submitted to *Clin Infect Dis*. Suppl in March 2019; under review for publication)

4. **Park S. E.,** Marks F. A conjugate vaccine against typhoid fever. *Lancet Infect Dis*. 14(2):90-1 (2014).

Co-authored manuscripts:

5. **GBD 2017 Typhoid and Paratyphoid Collaborators.** The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis*. pii: S1473-3099(18)30685-6. doi: 10.1016/S1473-3099(18)30685-6 (2019).

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The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa

Se Eun Park et al.#

There is paucity of data regarding the geographical distribution, incidence, and phylogenetics of multi-drug resistant (MDR) *Salmonella* Typhi in sub-Saharan Africa. Here we present a phylogenetic reconstruction of whole genome sequenced 249 contemporaneous *S.* Typhi isolated between 2008-2015 in 11 sub-Saharan African countries, in context of the 2,057 global *S.* Typhi genomic framework. Despite the broad genetic diversity, the majority of organisms (225/249; 90%) belong to only three genotypes, 4.3.1 (H58) (99/249; 40%), 3.1.1 (97/249; 39%), and 2.3.2 (29/249; 12%). Genotypes 4.3.1 and 3.1.1 are confined within East and West Africa, respectively. MDR phenotype is found in over 50% of organisms restricted within these dominant genotypes. High incidences of MDR *S.* Typhi are calculated in locations with a high burden of typhoid, specifically in children aged <15 years. Antimicrobial stewardship, MDR surveillance, and the introduction of typhoid conjugate vaccines will be critical for the control of MDR typhoid in Africa.

Correspondence and requests for materials should be addressed to F.M. (email: fmarks@ivi.int). #A full list of authors and their affiliations appears at the end of the paper.

Typhoid fever is a systemic infection primarily caused by the bacterium *Salmonella enterica* serovar Typhi (*S.* Typhi). The organism only infects humans, with the disease being contracted by the ingestion of bacteria through contaminated food or water. The vast majority of the global burden of disease (21.7 million estimated cases annually with 217,000 fatalities)[1] is thought to arise in urban areas in low-middle income countries (LMICs) in South and Southeast Asia, but more recent data have shown a substantial burden of disease in urban and rural areas of sub-Saharan Africa[2]. Between 2010 and 2014, the Typhoid Fever Surveillance in Africa Programme (TSAP) conducted population-based surveillance for typhoid fever in thirteen sites in ten sub-Saharan African countries[3]. The TSAP study, which recruited 13,431 febrile patients, isolated 135 *S.* Typhi from nine countries and found notably high incidences of typhoid fever in Burkina Faso, Ghana, and Kenya[2].

Many antimicrobials remain effective for the treatment of typhoid fever. However, *S.* Typhi that exhibit resistance to empirical antimicrobials hamper successful therapy[4]. The phenomenon of antimicrobial resistance (AMR) in *S.* Typhi has been well described, and resistance to the traditional first-line antimicrobials, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (co-trimoxazole), were associated with large outbreaks in Asia in the 1980s and 1990s[5,6]. The emergence of resistance to these first-line antimicrobials in Asia, which was dominated by the H58 genotype (now renamed 4.3.1)[7,8], led to a change in typhoid treatment guidelines, with fluoroquinolones becoming the empirical choice for MDR infections[9,10]. However, this shift towards the more common use of fluoroquinolones was inevitably followed by a decline in susceptibility to this group of antimicrobials[4,11].

Recent phylogenetic analyses further suggest that the multidrug resistant (MDR) *S.* Typhi genotype 4.3.1 dominates and circulates across Southeast (lineage I: Vietnam, Cambodia, and Laos) and South Asia (lineage II: mostly India with clusters in Nepal and Pakistan)[12]. Additionally, these 4.3.1 *S.* Typhi have transferred from South Asia into Eastern and Southern Africa (lineages I and II; Kenya, Tanzania, Malawi, South Africa)[12–14]. The characteristics of 4.3.1 *S.* Typhi define this genotype as a key driving force in global MDR *S.* Typhi, as intercontinental transmission, regional circulation, and multiple localised outbreaks over the last three decades are distinct from the evolutionary trends and population structure of other extent *S.* Typhi genotypes[12,15]. Despite the known circulation of 4.3.1 *S.* Typhi in sub-Saharan Africa, there is a paucity of data regarding the geographical distribution of AMR genotypes (MDR and reduced fluoroquinolone susceptibility), their phylogenetic structure, and the incidence of MDR typhoid fever across the African continent. Here, we aimed to investigate the phylogeography and incidence of MDR *S.* Typhi across sub-Saharan Africa, utilizing organisms generated through the TSAP initiative[2,3] and additional typhoid fever studies conducted in Ghana, Uganda, and The Gambia.

Results

Geographical distribution of *S.* Typhi genotypes in Africa. Phylogenetic analysis of 249 contemporary African *S.* Typhi genome sequences combined with 2,057 existing *S.* Typhi genome sequences (including 504 from Africa) permitted a visualisation of these new African isolates within a global *S.* Typhi genomic framework (Fig. 1). The primary observation was that these 249 contemporary African *S.* Typhi sequences were distributed throughout this framework, with multiple lineages found to be circulating simultaneously across sub-Saharan Africa in the last decade. With TSAP providing expansive sampling across the continent, we observed a substantial degree of genetic diversity, with 12 different *S.* Typhi genotypes represented in 11 different typhoid endemic countries (Fig. 2). This distribution of genotypes ranged from single organisms in particular countries (for example: The Gambia, Kenya, and Uganda) to numerous closely related organism clusters isolated in several countries (Supplementary Table 1).

Despite the apparent broad genetic diversity in the circulating *S.* Typhi population, the majority of the recently isolated organisms (225/249; 90%) belonged to only three genotypes, 4.3.1 (H58) (99/249; 40%), 3.1.1 (97/249; 39%), and 2.3.2 (29/249; 12%). Organisms belonging to genotype 4.3.1 were found only in East Africa, comprising 100% of the *S.* Typhi isolates from Kenya (59/59) and Uganda (30/30), and 91% (10/11) of the isolates from Tanzania (Fig. 1 and Fig. 2). Conversely, all of the organisms belonging to genotype 3.1.1 were found only in West African sites, constituting 88% (89/101) and 57% (8/14) of the *S.* Typhi organisms sequenced from Ghana and Burkina Faso, respectively. Organisms belonging to genotype 2.3.2 were found only in the West African countries of Burkina Faso, The Gambia, Ghana, Guinea-Bissau, and Senegal (Fig. 2 and Supplementary Table 1).

MDR phenotypes restricted to dominant *S.* Typhi genotypes. The MDR phenotype was prevalent across isolates from the 11 sampled countries, with 129/249 (52%) of all isolates exhibiting the classical *S.* Typhi MDR phenotypic profile of resistance against ampicillin, chloramphenicol, and co-trimoxazole. MDR organisms were widely distributed in both East and West Africa, and isolated in Ghana (68/101; 67%), Kenya (50/59; 85%), Tanzania (4/11; 36%), and Uganda (7/30; 23%). No MDR organisms were identified in Burkina Faso (0/14), Ethiopia (0/2), The Gambia (0/11), Guinea-Bissau (0/3), Madagascar (0/8), Senegal (0/8), or South Africa (0/2), and none of the organisms in these countries were genotype 4.3.1 or 3.1.1 except for Burkina Faso (8/14; genotype 3.1.1) (Fig. 2 and Table 1).

Saliently, MDR phenotypes were confined entirely within the dominant circulating genotypes in East (4.3.1) and West Africa (3.1.1). Overall, 70% (68/97) of 3.1.1 *S.* Typhi and 62% (61/99) of 4.3.1 *S.* Typhi were MDR (Supplementary Table 1). Further investigation revealed distinct origins of these MDR *S.* Typhi genotypes in each region. These contemporary genome sequences were compared to the existing global framework for *S.* Typhi 4.3.1 using a maximum likelihood phylogeny[12] (Fig. 3a). Our Kenyan MDR 4.3.1 organisms (2012–2013) belonged to two distinct clades, one in lineage I and the other in lineage II, indicative of the two distinct introductions from South Asia, as identified in an earlier global study[12], followed by the establishment of local populations. The Tanzanian MDR 4.3.1 organisms (2011–2012) clustered within each of these Kenyan clades, providing evidence of historical transfer of 4.3.1 *S.* Typhi from Kenya into Tanzania; ongoing local expansion was evident in the lineage I group only. The MDR 4.3.1 *S.* Typhi isolated in Uganda in 2015 formed a monophyletic clade within lineage II that was not closely related to the Kenyan or Tanzanian lineage II organisms, and were characterised by extremely narrow genetic diversity (mean pairwise genetic distance of 1 SNP), indicative of a recent population expansion or an outbreak[16]. This Ugandan MDR cluster was nested within a clade of 4.3.1 MDR *S.* Typhi organisms isolated in South Asia between 2007 and 2011, consistent with a third importation of MDR *S.* Typhi into East Africa from South Asia (Fig. 3a).

In contrast, the 3.1.1 MDR *S.* Typhi from Ghana (68 isolates) represented a population that was found only in West Africa, with the resulting phylogeny showing no evidence for intercontinental transmission as observed for 4.3.1 (Table 1). Rather, 3.1.1 *S.* Typhi could be better defined as a repeating pattern of

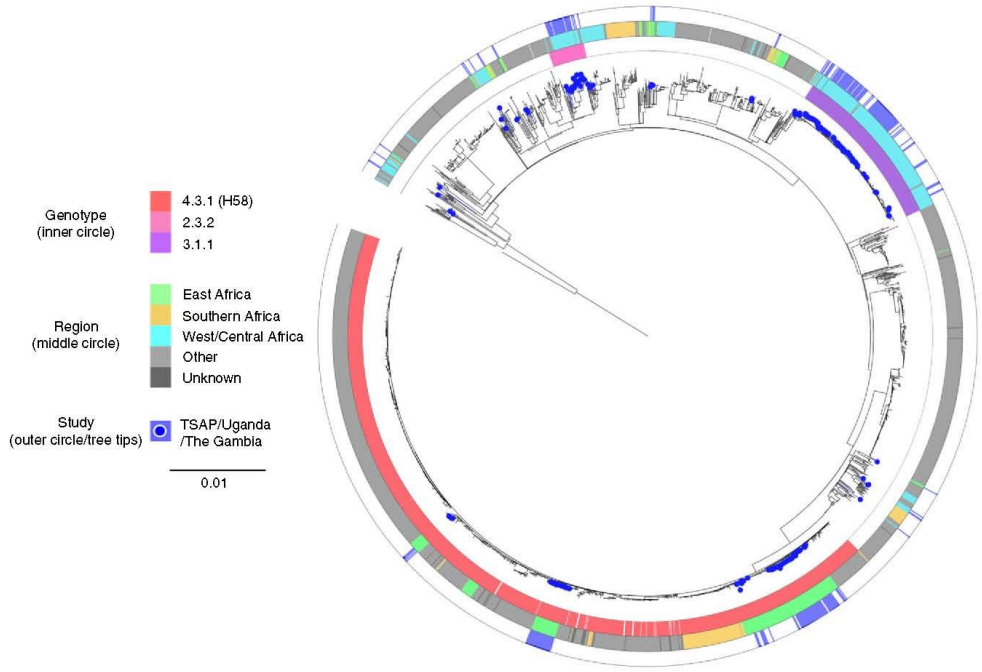

Fig. 1 The phylogenetic context of *Salmonella* Typhi isolated in sub-Saharan Africa. Maximum likelihood tree outlining the phylogenetic structure of 249 *S.* Typhi isolates unique to this study (highlighted by the blue points) combined with 2,057 global *S.* Typhi isolates. The tree is adjacent to three concentric circles highlighting associated metadata. The inner most circle represents the three most predominant genotypes (colour coded according to top of key), the middle circle represents the geographical sub-regions of Africa from where the *S.* Typhi organisms were isolated (colour coded according to top of key), and the outer circle (blue) again highlights the organisms unique to this study. The scale bar indicates the number of substitutions per variable site

small country specific population expansions with organisms being regularly transferred between countries (Fig. 3b). Phylogeographical reconstruction has not previously been performed for *S.* Typhi 3.1.1, therefore we conducted a Bayesian spatiotemporal phylodynamics analysis for the subclade using BEAST2 (Fig. 3b). The results suggest that Ghana was the most likely recent source of this 3.1.1 *S.* Typhi population (posterior probability = 0.66) which emerged de novo, and the corresponding source of three major clusters, which then radiated into other nearby countries on multiple occasions. Notably, Ghanaian *S.* Typhi appear to have been the probable origin of 3.1.1 *S.* Typhi in Burkina Faso on at least two separate occasions. Furthermore, existing whole genome sequences of 131 *S.* Typhi from Nigeria, including two isolates from travellers returning to the United Kingdom from Nigeria, demonstrated that 3.1.1 *S.* Typhi has been introduced into Nigeria from Ghana on at least two separate occasions. One of these events, estimated to be between 2010 and 2011, formed a major population expansion encompassing the majority (76/86; 88%) of the isolates from Nigeria.

Geographically distinct *S.* Typhi IncHI1 MDR plasmids. We next investigated the genetic mechanisms associated with the MDR phenotypes by inferring AMR gene content in the 249 contemporaneous African *S.* Typhi genome sequences. Across the dataset we identified genes encoding resistance to aminoglycosides (*aph(3'')-Ib*, *aph(6)-Id*, and *ant(3'')-Ia*), ampicillin (OXA-1 and TEM-95/-93), chloramphenicol (*catA1*), trimethoprim (*dfrA7*, *dfrA14* and *dfrA15*), sulfonamides (*sul1* and *sul2*), and tetracycline (*tet(A)* and *tet(D)*). Most AMR genes were associated with IncHI1 plasmids. However, the two MDR *S.* Typhi genotypes were associated with distinct plasmid lineages. The 3.1.1 MDR *S.* Typhi from Ghana (68 isolates) carried IncHI1 MDR plasmids of plasmid sequence type (PST) 2a, whilst the 4.3.1 MDR *S.* Typhi from Kenya (50 isolates) and Uganda (7 isolates), respectively carried ST6 and ST6a IncHI1 MDR plasmids. Minor differences in the specific AMR genes were also evident between these plasmid types (Fig. 4). For example, the class I integron cassette contained *dfrA15* in the West African/PST 2a plasmid and *dfrA7* in East African/PST 6/6a plasmids, the latter plasmids also contained *sul2* and *tet(D)* which were absent from the West African isolates.

Outliers included: non-MDR *S.* Typhi isolates from Burkina Faso (genotype 2.2) with an IncX1 plasmid containing no resistance genes and Ghana (genotype 3.1.1) with an IncN plasmid displaying resistance against aminoglycosides (*aph(6)-Id*), ampicillin (TEM-95/-93), trimethoprim (*dfrA14*), and sulfonamides (*sul2*) and 5 non-MDR *S.* Typhi isolates (genotype 4.3.1) from Tanzania with IncFIB plasmid carrying resistant genes *aph(3'')-Ib*, *aph(6)-Id*), TEM-95/-93, *dfrA14*, *sul2*; and an MDR *S.* Typhi isolate (genotype 4.3.1) from Kenya with an IncHI1 and IncQ1 plasmid associated with resistance genes against aminoglycosides (*aph(3'')-Ib*, *aph(6)-Id*), ampicillin (TEM-95/-93), chloramphenicol (*catA1*), trimethoprim (*dfrA7*),

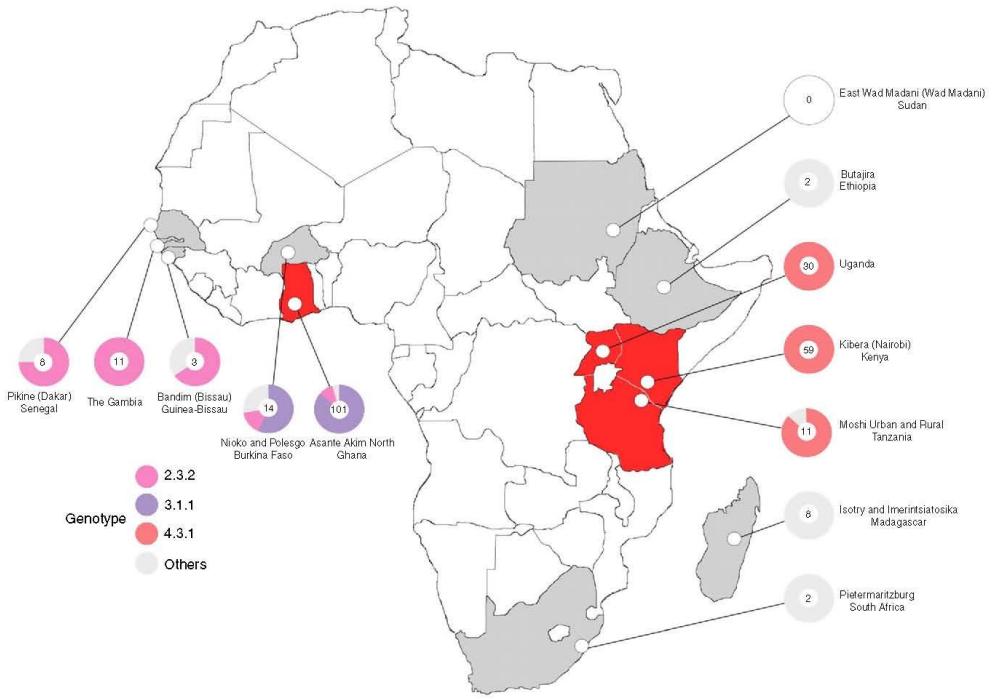

Fig. 2 The distribution of multi-drug resistant *Salmonella* Typhi isolated in Africa. Map of the African continent showing the locations of the field sites from where the S. Typhi organisms were isolated for this study. Countries in which multi-drug resistant (MDR) S. Typhi were isolated are coloured in red, countries in which MDR S. Typhi were not isolated are coloured in grey. Pie charts correspond with the proportion of the main genotypes isolated (see key), with the number of isolates from each location in the centre

sulfonamide (*sul1* and *sul2*), and tetracycline (*tet(A)* and *tet(D)*) (Fig. 4). Additionally, none of the four MDR organisms from Tanzania possessed a detectable plasmid backbone. Using Bandage to investigate the location of MDR cassettes, we found that these isolates carried multiple resistance genes (*aph(3'')-Ib*, *aph(6)-Id*), TEM-95/-93, *catA1*, *dfrA7*, *sul1*, *sul2)* on a 24-kb composite chromosomal transposon (Tn2670-like element) inserted between coding sequences STY3618 and STY3619[12].

In total, 16% (39/249) of the contemporaneous African *S.* Typhi exhibited reduced susceptibility against ciprofloxacin (9 from Kenya and 30 from Uganda). The Kenyan organisms exhibited the common mutation associated with reduced susceptibility to fluoroquinolones in *S.* Typhi, a substitution from serine to phenylalanine at codon 83 (Ser83Phe) in *gyrA*. The Ugandan organisms harboured an alternative serine to tyrosine *gyrA* mutation also at codon 83 (Ser83Tyr) (Table 1).

The incidence of MDR typhoid fever in African countries. We lastly calculated the incidence of MDR typhoid fever in specific age groups in countries where MDR *S.* Typhi was isolated: Ghana, Kenya, and Tanzania (Table 2). The incidence of MDR *S.* Typhi exceeded 100/100,000-person years of observation (PYO) in specific age groups in Ghana (<15 years: 414/100,000 PYO; 95% confidence interval [CI], 333–515) and Kenya (<15 years: 398/100,000 PYO; 95% CI, 291–545), in all age groups in Kenya (263/100,000 PYO; 95% CI, 199–347) and in the urban site in Tanzania (103/100,000 PYO; 95% CI, 61–173). While Burkina Faso had a high overall incidence of typhoid[2], no MDR *S.* Typhi were detected; 2/14 isolates were resistant to chloramphenicol and co-trimoxazole. The highest incidence of MDR *S.* Typhi in a specific age group in a single location was in children aged 2–4 years in Ghana (747/100,000 PYO; 95% CI, 491–1135), followed by 5–14 year olds in Kenya (507/100,000 PYO; 95% CI, 352–729). In Kenya and Ghana, the only TSAP sites where *S.* Typhi were isolated from infants (aged 0–1 years), the incidences of MDR *S.* Typhi in this age group were 148 (95% CI, 48–458) and 60 (95% CI, 17–210) per 100,000 PYO, respectively. Generally, the incidence of MDR *S.* Typhi was substantially higher in children <15 years than in adults. An exception was in Tanzania, where MDR *S.* Typhi occurred in higher incidences in those aged ≥15 years than in young children (Table 2).

Discussion

Here we present a contemporary dataset of *S.* Typhi genome sequences and AMR data from across sub-Saharan Africa generated through a major population-based surveillance study with data augmented from further locations. We exploited these data to assess the circulation of MDR *S.* Typhi genotypes and to calculate the incidence of MDR typhoid infections across the continent. Our results have major implications for the use of empirical antimicrobials for treating febrile disease of presumed bacterial origin and future intervention measures for controlling typhoid in Africa.

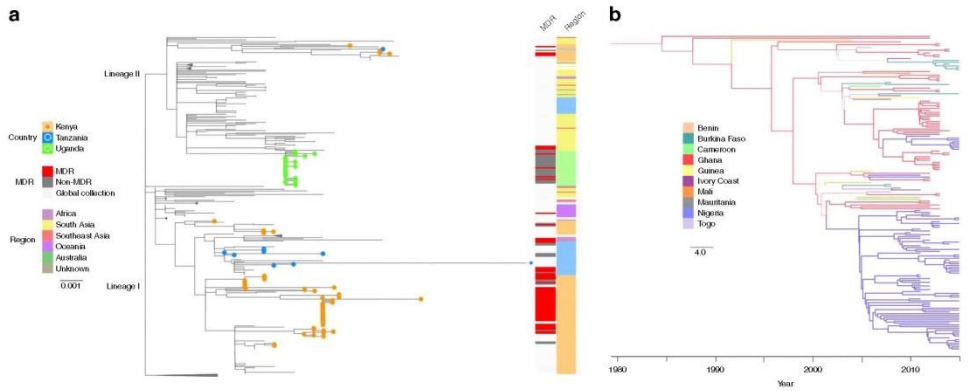

Fig. 3 The phylogenetic structures of the major *Salmonella* Typhi genotypes in sub-Saharan Africa. **a** Maximum likelihood tree of genotype 4.3.1 *S.* Typhi isolates from this study in the context of other global genotype 4.3.1 *S.* Typhi isolates; the two distinct sub-lineages are labeled at the base of the tree. 4.3.1 *S.* Typhi isolates from this study (Kenya, Tanzania, and Uganda) are highlighted in corresponding coloured branches and circles at the tip of each tree. The first coloured bar shows the MDR phenotypes of study isolates. The second coloured bar outlines the continents and African regions where 4.3.1 *S.* Typhi have been detected. Scale bar indicates the number of substitutions per variable site; nodes of the tree have been collapsed for better visualization. **b** Maximum clade credibility tree (reconstructed using BEAST2) of genotype 3.1.1 *S.* Typhi isolates from this study in the context of other global genotype 3.1.1 *S.* Typhi isolates. Tree shows a phylogeographical reconstruction of genotype 3.1.1 *S.* Typhi isolates in West Africa. Branches are weighted by the support for the location changes; thicker branches have higher support. Branches and nodes are coloured according to the location that had the highest posterior probability values for some nodes of the tree. The scale bar indicates the number of substitutions per variable site per year

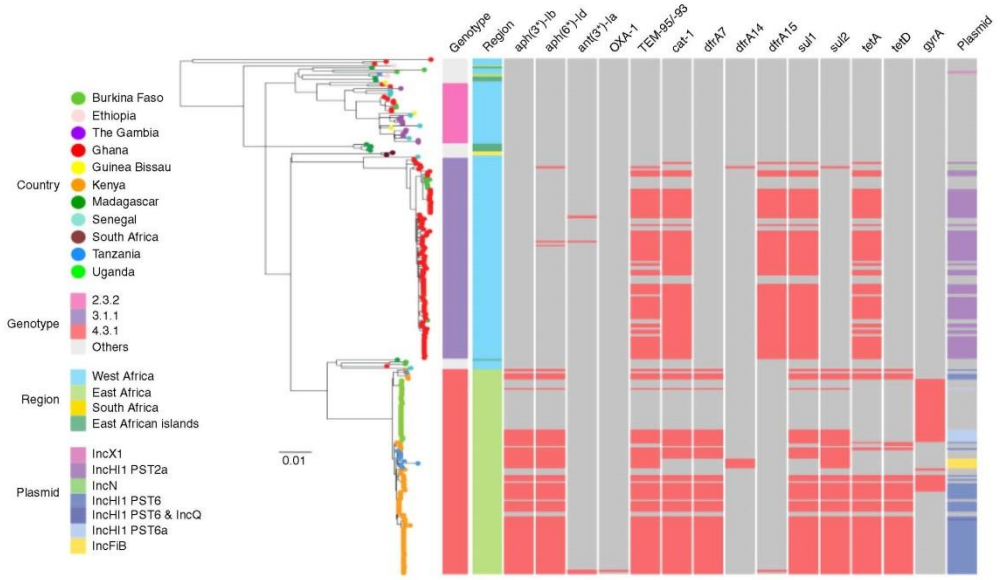

Fig. 4 The antimicrobial gene distribution within sub-Saharan African *Salmonella* Typhi. Maximum likelihood phylogenetic tree of 249 *S.* Typhi isolates from this study with corresponding metadata including genotype, location, antimicrobial resistance genes (AMR), and plasmids (see keys). Countries where *S.* Typhi isolates were isolated are highlighted by coloured circles at the tip of the branches. The three major genotypes and sub-regions of the Africa continent are shown by the coloured bars; present AMR genes are shown in red. The scale bar indicates the number of substitutions per variable site

Table 1 Genotypes of MDR[a] *S.* Typhi and *gyrA* in four countries[b]

Country (n, all *S.* Typhi per country)	MDR *S.* Typhi (*n*)	MDR *S.* Typhi (%/out of all *S.* Typhi per country)	MDR *S.* Typhi Genotype	Non-susceptible to fluoroquinolones (*n*, *gyrA*)[c]
Ghana (101)	68	67	3.1.1	0
Kenya (59)	50	85	4.3.1 (H58)	9 (Ser83Phe)
Tanzania (11)	4	36	4.3.1 (H58)	0
Uganda (30)	7	23	4.3.1 (H58)	30 (Ser83Tyr)
Total 201 *S.* Typhi from 4 countries (out of 249 *S.* Typhi from 11 countries[d])	129	64% of 201 52% of 249		

[a]MDR definition used for the analysis: presence of resistant genes for at least one agent in all three antimicrobial categories of ampicillin/amoxicillin (beta-lactamase: OXA-1, TEM-95/-93) AND chloramphenicol (*catA1*), AND trimethoprim-sulfamethoxazole (sulfonamide (*sul1, sul2*) and trimethoprim (*dfrA7, dfrA14, dfrA15*)

[b]Four countries with MDR *S.* Typhi organisms: Ghana, Kenya, Tanzania, and Uganda

[c]Out of total 249 *S.* Typhi isolates yielded from this study in 11 countries in sub-Saharan Africa, total 39 isolates were non-susceptible to fluoroquinolone (ciprofloxacin and nalidixic acid (*gyrA*): 9 of 39 isolates were from Kenya, of which 7 were MDR *S.* Typhi; and all 30 isolates from Uganda were non-susceptible to fluoroquinolones, of which 7 were MDR *S.* Typhi. These 39 organisms exhibited the mutations at codon 83 of *gyrA*; serine (TCC) to phenylalanine (TTC) for all 9 isolates from Kenya (Ser83Phe) and serine (TCC) to TAC (tyrosine) for all 30 Uganda isolates (Ser83Tyr)

[d]No MDR *S.* Typhi from Burkina Faso (14; genotypes 2.2 (2 isolates), 2.3.2 (2 isolates), 3.1.1 (8 isolates), and 4.1.1 (2 isolates)), Ethiopia (2; genotypes 1.2 (1 isolate) and 2.2.2 (1 isolate)), Gambia (11 isolates, all genotype 2.3.2), Guinea-Bissau (3; genotypes 2.3.2 (2 isolates) and 2.3.1 (1 isolate), Madagascar (8; genotypes 2.5 (4 isolates), 2.2 (3 isolates), and 4.1 (1 isolate)), Senegal (8; genotypes 2.3.2 (6 isolates), 3.1 (1 isolate), and 4.1 (1 isolate)), and South Africa (2; all genotypes 3.1.1)

Table 2 The incidence of MDR typhoid fever in sub-Saharan Africa[a]

Country	Age group in years	PYO estimation[b]				Recruitment proportion[b]	Genome-sequenced *S.* Typhi cases[c]	Crude MDR *S.* Typhi cases	Crude MDR *S.* Typhi incidence per 100,000 PYO	Adjusted MDR *S.* Typhi cases	Adjusted MDR *S.* Typhi incidence per 100,000 PYO (95% CI)[d]
		Proportion of catchment population visiting study facility in case of fever (95% CI)	Catchment population	Catchment population adjusted by health-seeking behavior	PYO						
Ghana[e]											
AAN	0–1	16% (14–18)	11222	1760	4080	41%	1	1	25	2	60 (17–210)
	2–4	16% (13–18)	8086	1268	2940	41%	17	12	306	22	747 (491–1135)
	0–4	n.a.	n.a.	n.a.	n.a.	n.a.	18	13	n.a.	n.a.	n.a.
	5–14	16% (15–17)	34439	5415	12554	623/1657 (38%)	23	16	96	24	252 (177–357)
	<15	n.a.	53747	8443	19574	n.a.	41	29	97	81	414 (333–515)
	≥15	n.a.	n.a.	n.a.	n.a.	n.a.	22	16	n.a.	n.a.	n.a.
	Non_TSAP[e]	n.a.	n.a.	n.a.	n.a.	n.a.	38	23	n.a.	n.a.	n.a.
	All	n.a.	n.a.	n.a.	n.a	n.a.	101	68	n.a.	n.a.	n.a.
Kenya											
Kibera	0–1	42% (38–47)	3467	1456	2031	99/99 (100%)	5	3	148	3	148 (48–458)
	2–4	39% (36–43)	3070	1197	2039	312/312 (100%)	11	7	343	7	343 (164–720)
	5–14	43% (39–47)	7514	3231	5722	539/539 (100%)	32	29	507	29	507 (352–729)
	<15	n.a.	14051	5884	9792	n.a.	48	39	398	39	398 (291–545)
	≥15	35% (32–38)	15263	5342	9228	301/301 (100%)	11	11	119	11	119 (66–215)
	All	n.a.	29314	11227	19020	n.a.	59	50	263	50	263 (199–347)
Tanzania[f]											
Moshi Rural	0–1	4% (0–11)	24289	390	693	79%	0	0	0	0	0
	2–4	2% (0–4)	25281	406	721	79%	0	0	0	0	0
	5–14	13% (10–16)	118219	15487	27508	79%	1 (2)[f]	0	0	0	0
	<15	n.a.	167789	16283	28922	n.a.	1 (2)[f]	0	0	0	0
	≥15	2% (1–2)	298948	5172	9186	79%	2 (4)[f]	0	0	0	0
	All	n.a.	466737	21454	38108	n.a.	3 (6)[f]	0	0	0	0
Moshi Urban	0–1	7% (0–19)	10406	335	595	79%	0	0	0	0	0
	2–4	2% (0–6)	10831	348	618	79%	0	0	0	0	0
	5–14	13% (8–19)	37309	4850	8615	79%	3 (9)[f]	2 (7)[f]	12 (81)[f]	1 (9)[f]	15 (3–84) (103 (54–199))[f]
	<15	n.a.	58546	5533	9828	n.a.	3 (9)[f]	2 (7)[f]	10 (71)[f]	1 (9)[f]	10 (1–72) (91 (47–175))[f]
	≥15	n.a.	125746	2138	3796	79%	4 (8)[f]	2 (4)[f]	53 (105)[f]	3 (5)[f]	67 (19–229) (133 (56–319))[f]
	All	n.a.	184292	7671	13626	n.a.	7 (17)[f]	4 (11)[f]	29 (81)[f]	4 (14)[f]	29 (11–78) (103 (61–173))[f]

[a]The TSAP study has data from total 10 countries, of which 9 countries (Burkina Faso, Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, and Tanzania in alphabetical order) found blood culture confirmed *S.* Typhi isolates circulating in the respective sites. These *S.* Typhi isolates have been whole-genome sequenced for detection of multidrug resistant (MDR) genes. In addition, *S.* Typhi isolates yielded from 2 other surveillance activities in Uganda and The Gambia have been added to this analysis. Of these 11 countries, *S.* Typhi isolates with MDR genes were detected in Ghana from West Africa and Kenya, Tanzania, and Uganda from East Africa. Incidence of MDR *S.* Typhi in Uganda could not be estimated due to insufficient data on age stratification of patients, catchment population, healthcare seeking behavior and recruitment proportion, which were applied uniformly for the analysis presented in this table for Ghana, Kenya, and Tanzania

[b]PYO estimation and recruitment proportion have been published in detail in the TSAP typhoid burden paper (Marks et al, Lancet Global Health, 2017).

[c]Genome sequenced *S.* Typhi case numbers in this table may not exactly match the crude *S.* Typhi case numbers reported in the TSAP typhoid burden paper (Marks et al) due to few sequencing failures

[d]Adjusted incidence rates per 100,000 PYO (95% CI): adjustments for case recruitment and error factors

[e]Ghana samples include non-TSAP projects as outlined in the Supplementary Table 2. AAN: Asante Akim North (Supplementary Table 2)

[f]Tanzania: Enrolment algorithm has been applied to the crude MDR *S.* Typhi case numbers, that is: recruitment by every 5th patient if enrolled before Nov 11th 2011 and every 2nd patient if enrolled after then. 1 isolate from Tanzania, which was from outside the study catchment area (Supplementary Table 2: "Moshi Other") is not included in this incidence table due to the insufficient background data required as mentioned in this footnote

Despite the broad genetic diversity observed within the continental *S.* Typhi population, we identified only three principal *S.* Typhi genotypes. These genotypes were geographically limited to East (genotype 4.3.1) and West (genotypes 3.1.1 and 2.3.2) Africa. MDR *S.* Typhi in Africa is currently dominated by genotypes 4.3.1 and 3.1.1. *S.* Typhi 4.3.1 has been previously reported to circulate only in East Africa on the African continent[12–14], with 3.1.1 dominating in Nigeria and circulating amongst neighbouring countries in West Africa[17]. After the likely importation from South Asia within the last 20 years, the extant population of *S.* Typhi 4.3.1 in Kenya, Tanzania, and Uganda has been formed through multiple introductions from South Asia followed by local expansions. Conversely, *S.* Typhi 3.1.1, which were isolated in Ghana, Burkina Faso, and Nigeria, do not appear to have recent ancestral roots in Asia, but have undergone localised microevolution within West Africa in recent decades. We speculate that these organisms have been transferred, maintained, and selected through the sustained movement of people and antimicrobial usage in West Africa. The MDR 4.3.1 *S.* Typhi from Kenya and Uganda also commonly exhibited mutations in *gyrA*, associated with reduced susceptibility to fluoroquinolones, which has also been reported in Africa in recent years. Conversely, no *gyrA* mutations were found in the MDR *S.* Typhi 3.1.1 from Ghana. These data mirror recent reports from Nigeria[17], and suggest that first-line antimicrobial agents (ampicillin, chloramphenicol, and co-trimoxazole) for the treatment of febrile diseases are still in common use in West Africa.

The acquisition of an MDR phenotype in *S.* Typhi is typically associated with IncHI1 plasmids, which have long been considered the main vehicle for resistance to first-line antimicrobials in *S.* Typhi[8]. The distinct MDR lineages of *S.* Typhi found in West and East Africa, each associated with a distinct IncHI1 plasmid sequence type, suggest that *S.* Typhi and its AMR plasmids have not been transferred laterally across the continent. This may be because genotype 4.3.1 MDR *S.* Typhi has not been circulating for a sufficient period in Africa to reach the West African region. Furthermore, the four MDR *S.* Typhi isolates from Tanzania did not harbour plasmid-associated sequences, suggesting that these AMR genes are inserted into the chromosome, as has been observed previously in Asia[12,18,19] and Zambia[20]. The integration of AMR genes into the *S.* Typhi chromosome is a worrying development, as it provides a mechanism for stable vertical transmission of the MDR phenotype without the potential fitness deficit associated with maintaining large plasmids, increasing the likelihood that MDR will be sustained during the ongoing spread of related *S.* Typhi across East Africa.

Here we identified specific populations that are most at risk of MDR typhoid, which particularly warrants a reconsideration of current empirical antimicrobial use for treatment of typhoid. Generally, we found that the site incidences of MDR *S.* Typhi corresponded largely with the overall burden of typhoid in the various study sites[2] (that is, countries with high incidences of typhoid also had high incidences of MDR *S.* Typhi). Consequently, Kenya and Ghana exhibited the highest incidences of MDR typhoid in the sampled countries. Notably, Burkina Faso, which had a high burden of typhoid, had no incidence of MDR *S.* Typhi in comparison to neighbouring Ghana. Further, we found that children aged <15 years, the highest at-risk age group for typhoid in Africa, also generally exhibited the highest incidence rates of MDR *S.* Typhi infections. This age distribution of typhoid caused by MDR *S.* Typhi was not consistent across the continent, as those aged >15 years in Tanzania exhibited a higher incidence of MDR *S.* Typhi than younger children. Alternatively, some sites with a high burden of typhoid in specific age groups had no MDR infections. We suggest that this distribution is likely to mirror access to, and the generic usage of, specific antimicrobial agents in these locations and age groups, warranting the need for continued country/site-specific surveillance, review of local treatment policies, and the collection of antimicrobial usage data.

The incidence of MDR typhoid varied dramatically between settings and also between age groups in some individual locations. This discrepancy may be due to differing exposures to antimicrobials in different settings and age groups, which could lead to differential selective pressures in local circulating bacterial populations. Our data additionally indicate that AMR/MDR *S.* Typhi are not only spread through local population movements in East and West Africa but can also arise de novo. This phenomenon can be observed within the microevolution and expansion of 3.1.1 MDR *S.* Typhi in West Africa. The AMR genes associated with 4.3.1 MDR *S.* Typhi in East Africa appear to be both plasmid and chromosomally located. This observation, coupled with the acquisition of reduced susceptibility to fluoroquinolones, transmission between East African countries, and the importation of organisms from South Asia, raises further concerns regarding the progression of drug resistant *S.* Typhi in Africa. 4.3.1 *S.* Typhi has spread successfully cross South Asia and become increasingly resistant to ciprofloxacin, making treatment options more limited[4]. The pervasiveness of AMR in 4.3.1 *S.* Typhi in South Asia has been recently highlighted by an outbreak of a ceftriaxone-resistant 4.3.1 *S.* Typhi in Hyderabad, Pakistan, which appears to be resistant to commonly available antimicrobial classes[21]. We predict that new AMR phenotypes that emerge in 4.3.1 *S.* Typhi in Asia can be periodically introduced into East Africa. Further, the emergence of MDR *S.* Typhi 4.3.1 in South Africa suggests possible spread from East Africa to Southern Africa through human population movement, however this notion requires further investigation[22].

This study highlights locations in sub-Saharan Africa where MDR typhoid is prevalent and where future activities to control its spread from Asia into Africa and also within Africa could be focused. In addition to continuing disease surveillance and investigating the genomic characteristics and phenotypic profiles of MDR *S.* Typhi, compiling antimicrobial usage data that can be linked with the distribution of AMR/MDR bacterial pathogens across Africa is becoming essential. The World Health Organization (WHO) has prequalified a typhoid conjugate vaccine (TCV) in January 2018 with a recommendation to introduce the vaccine for infants and children older than six months in typhoid endemic countries[23]. Targeted vaccination programs at sites with a high burden of AMR/MDR *S.* Typhi could also be considered and may be informed by the age-stratified MDR disease incidence data presented here. New and potentially highly efficacious *S.* Typhi conjugate vaccines are currently undergoing clinical trials and should become routinely available at the end of this decade[23]. Until these vaccines become available, countries in Africa with endemic typhoid should structure antimicrobial stewardship policies to control MDR *S.* Typhi and develop national roadmaps for their deployment.

Methods

Bacterial isolates and antimicrobial susceptibility testing. Between 2010 and 2014, a population-based surveillance of invasive *Salmonella* infections was conducted in ten sub-Saharan countries (see Supplementary Table 2)[2]. The research methodology including ethics approvals, sampling framework, and calculation of disease incidence of this programme have been previously reported[3]. Briefly, over the TSAP sampling period, blood culture-based surveillance was conducted in defined catchment areas. Cultured isolates were assessed for antimicrobial susceptibilities by the disc diffusion method locally and at a central reference laboratory. TSAP recruited 13,558 patients meeting the study inclusion criteria, of which 127 patients were excluded due to incomplete data. This resulted in 13,431 patients and 135 *S.* Typhi found in 9 countries for analysis[2]. We also included 114 additional *S.* Typhi collected from other studies in Africa (Uganda; 2015, Gambia; 2008-2014 and non-TSAP isolates from Ghana; 2010), resulting in a collection of 249 *S.* Typhi (Supplementary Table 2).

Genome sequencing and SNP calling. Genomic DNA from the 249 *S.* Typhi isolates was extracted using the Wizard Genomic DNA Extraction Kit (Promega, Wisconsin, USA). Two μg of genomic DNA from each organism was subjected to indexed-tagged pair-end sequencing on an Illumina Hiseq 2000 platform (Illumina, CA, USA) to generate 100 bp paired-end reads. To identify single nucleotide polymorphisms (SNPs), raw Illumina reads were mapped to the reference sequence of *S.* Typhi CT18 (accession: AL513382) including plasmids pHCM1 (accession: AL513383) and pHCM2 (accession: AL513384), using SMALT version 0.7.4. Candidate SNPs were called against the reference sequence using SAMtools[24] and filtered with a minimal phred quality of 30 and minimum consensus base agreement of 75%. The allele at each locus in each isolate was determined by reference to the consensus base in that genome using SAMtools *mpileup* and removing low confidence alleles with consensus base quality ≤20, read depth ≤5 or a heterozygous base call. SNPs in phage regions, repetitive sequences, or recombinant regions identified previously were excluded[12,25]. We further identified an additional recombinant region from the whole genome alignment produced by SNP-calling isolates using Gubbins[26] and SNPs detected within this region (~20kb from nucleotide 1,439,032-1,459,472) were removed, resulting in a final set of 4,444 chromosomal SNPs. The SNP data were used to assign all isolates to previously defined subclades in the *S.* Typhi genotyping framework[15].

Phylogenetic analysis. A maximum likelihood (ML) phylogenetic tree was constructed from the 4,444 SNP alignment using RAxML version 8.2.8 with a generalized time-reversible model and a Gamma distribution to model the site-specific rate variation (GTR+Γ_4 model)[27]. Branch support for this tree was assessed through a bootstrap analysis with 1,000 pseudo-replicates. To investigate the molecular epidemiology of our African isolates in regional and international context, a secondary ML tree was inferred from a separate alignment of 26,479 SNPs identified across a total of 2,306 *S.* Typhi isolates (249 from this study, 1,830 from the global collection[12], 128 from Nigeria[17], and 99 travel-associated *S.* Typhi organisms isolated in the United Kingdom[15]) using RAxML with GTRGAMMA substitution model and *S.* Paratyphi A sequence data to outgroup root the tree. Branch support for this phylogeny was assessed through a 100 bootstrap pseudo-analysis. Annotation of this global tree was visualized using ITOL[28]. An interactive version of the global phylogeny, with organisms labeled by genotype, country of origin, year of isolation and antimicrobial susceptibility was generated in Microreact[29].

Evolutionary timescale and phylogeographic patterns. For genotype 3.1.1 strains, Bayesian phylogenetic analyses was conducted in BEAST2 v2.4.7[30]. The GTR+Γ_4 substitution model, an uncorrelated lognormal relaxed-clock model, and the exponential-growth coalescent tree prior were used. Three independent analyses were performed with 5×10^8 steps, recording samples every 5×10^4 steps. We assessed sufficient sampling by combining the three independent runs and verifying that the effective sample size of all parameters was at least 500. To calibrate the molecular clock, we used the sampling year of all sequences. This analysis also included an outgroup sequence (CT18) to ensure a biologically meaningful root location. Our selected molecular clock model and tree prior have been shown to perform well even when the data display low rate variation and constant population size dynamics[31]. This model combination also allows for informal model testing via the coefficient of rate variation and the population growth rate parameters[32,33]. To determine phylogeographic patterns, we considered the country of sampling as a discrete trait in our analysis in BEAST2[34]. A potential shortcoming of this analysis was that it includes a large number of parameters (transition rates between all locations), therefore the output of these analysis may be affected by the prior distribution. We verified that the prior distribution differed from the posterior by comparing the distributions of all transition rates.

An important consideration when using sampling times as calibrations is that the sampling timespan should capture sufficient genetic variation to allow reliable inferences of evolutionary rates and timescales, such that the data have strong temporal structure. We verified the temporal structure in the data by using a root-to-tip regression and a date-randomisation test[35]. We conducted a root-to-tip regression for the outgroup-rooted ML tree using TempEst[36], and obtained a positive value for the slope, an R^2 of 0.12, and a *p*-value of 3×10^{-6} (Supplementary Figure 1). For the date-randomisation test we repeated the analysis 20 times while randomising the sampling times. Our expectation was that the randomisations should produce evolutionary rate estimates that were lower and that did not overlap with those obtained with the correct sampling times[37], which was the case for our data (Supplementary Figure 2). Finally, we compared our estimate of the time of origin of the 3.1.1 lineage in BEAST with an independent method, LSD v0.3[38]. LSD and BEAST2 produced congruent estimates of the time of origin of the 3.1.1 lineage (Supplementary Figure 3).

Antimicrobial resistance gene and plasmid analyses. ARIBA (Antimicrobial Resistance Identifier by Assembly)[39] and CARD (https://card.mcmaster.ca/home) were used to investigate AMR gene content. ARIBA reported the AMR genes and the quality of assemblies and variants detected between the sequencing reads and the reference sequences, including mutations in the quinolone resistance-determining region (QRDR) of the *gyrA*, *gyrB*, *parC*, and *parE* genes. For plasmid identification, the sequence reads from each isolate were de novo assembled using the short-read assembler Velvet with parameters optimized by Velvet Optimizer[40,41]. Contigs that were less than 300 bp long were excluded and the assembled contigs were annotated using Prokka[41,42]. Plasmid typing was performed *in silico* using PlasmidFinder[43]. The presence of the IncHI1 plasmid was confirmed by BLASTN searching the assembled sequences in reference to the pHCM1 reference plasmid sequence, and comparative analyses were performed and visualized using ACT[44]. The IncHI1 plasmid sequence type was identified using SRST2 software[45] with the IncHI1 plasmid MLST scheme[46]. To investigate the isolates with MDR phenotype and without plasmid, raw sequences were subjected to *de novo* genome assembly using SPAdes[47] version 3.11.0, and the resulting assembly graph was visualized in Bandage[48] to inspect the location of AMR genes in the genome.

Incidence analyses of MDR *S.* Typhi. Incidence of MDR *S.* Typhi was estimated per 100,000 person-years of observation (PYO) for MDR *S.* Typhi isolates found in Ghana, Kenya and Tanzania. Statistical methodology used previously to calculate the incidence of *S.* Typhi TSAP isolates[2,3] was applied to calculate MDR *S.* Typhi incidence. Briefly, age-stratified PYO were estimated using available demographic data in HDSS (Health and Demographic Surveillance System) and non-HDSS sites and health-seeking behaviour of randomly selected individuals, representative of the study population, were factored in (denominator). The recruitment proportion was adjusted to the age-stratified crude MDR *S.* Typhi cases (numerator). Adjusted incidence of MDR *S.* Typhi per 100,000 PYO was estimated with 95% CIs using these adjustment factors and crude MDR *S.* Typhi case numbers. The previously established multi-country database (FoxPro software) for TSAP was used for the three countries with MDR *S.* Typhi. The incidence of MDR *S.* Typhi in Uganda could not be measured, as data regarding adjustment factors (healthcare seeking behaviour and recruitment proportion) was unavailable at the time of analysis.

Data availability

Raw sequence data are available in the European Nucleotide Archive (projects ERP009684, ERP010763, ERP013866). The Microreact interactive phylogeny of the analysed isolates is available at: https://microreact.org/project/HJWBihsvz. SMALT version 0.7.4 used is available at: http://www.sanger.ac.uk/resources/software/smalt/.

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Author contributions

S.E.P., D.P.T., C.B., V.K.W., G.D.P., S.D. and Z.D. contributed in data analysis, interpretation of results under the scientific guidance from S.B. and K.E.H. S.E.P. drafted and edited the paper and S.B. contributed in structuring and editing of the paper. F.M. contributed in project oversight. F.M., S.E.P., V.vK., L.M.C.E., U.P., G.D.P., J.I., H.S-G., J.A.C., R.F.B., Y.A-S., E.O-D., R.R., A.B.S., A.A., N.G., K.H.K., J.M., A.G.S., P.A., H.M.B., J.T.H., J.M.M., L.C., B.O., B.F., N.S., T.J.L.R., T.M.R., L.P.K., E.S., M.T., B.Y., M.A.E.T., A.S., S.P., A.T., A.N., M.B.A., S.V.L., H.J.S., H.J.J., J.F.D., J.K.P., F.K., P.H., J.N.S., T.V., R.D., U.N.I., G.A.M. and S.O. contributed to data acquisition in the field, interpretation of results, and editing of the paper. G.D., J.A.K., A.P., D.M.A., S.A., M.A. and J.D.C. contributed to data interpretation. All authors read and approved the final draft.

Additional information

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Se Eun Park[1,2], Duy Thanh Pham[2], Christine Boinett[2,3], Vanessa K. Wong[4,5], Gi Deok Pak[1], Ursula Panzner[1], Ligia Maria Cruz Espinoza[1], Vera von Kalckreuth[1], Justin Im[1], Heidi Schütt-Gerowitt[1,6], John A. Crump[7,8,9,10], Robert F. Breiman[11,12], Yaw Adu-Sarkodie[13,14], Ellis Owusu-Dabo[13,14], Raphaël Rakotozandrindrainy[15], Abdramane Bassiahi Soura[16], Abraham Aseffa[17], Nagla Gasmelseed[18,19], Karen H. Keddy[20,21], Jürgen May[22,23], Amy Gassama Sow[24,25], Peter Aaby[26,27], Holly M. Biggs[7,8], Julian T. Hertz[7,8], Joel M. Montgomery[11], Leonard Cosmas[11], Beatrice Olack[28], Barry Fields[11], Nimako Sarpong[13,23], Tsiriniaina Jean Luco Razafindrabe[15], Tiana Mirana Raminosoa[15], Leon Parfait Kabore[29], Emmanuel Sampo[29], Mekonnen Teferi[17], Biruk Yeshitela[17], Muna Ahmed El Tayeb[18], Arvinda Sooka[20], Christian G. Meyer[30,31], Ralf Krumkamp[22], Denise Myriam Dekker[22,23], Anna Jaeger[22], Sven Poppert[32], Adama Tall[25], Aissatou Niang[25], Morten Bjerregaard-Andersen[26,27], Sandra Valborg Løfberg[26,27], Hye Jin Seo[1], Hyon Jin Jeon[1], Jessica Fung Deerin[1], Jinkyung Park[1], Frank Konings[1], Mohammad Ali[1,33], John D. Clemens[1,34,35], Peter Hughes[36], Juliet Nsimire Sendagala[36], Tobias Vudriko[36], Robert Downing[37,38], Usman N. Ikumapayi[39], Grant A. Mackenzie[39,40,41], Stephen Obaro[42,43,44], Silvia Argimon[4], David M. Aanensen[4,45], Andrew Page[4], Jacqueline A. Keane[4], Sebastian Duchene[46], Zoe Dyson[46], Kathryn E. Holt[46], Gordon Dougan[4,47], Florian Marks[1,47] & Stephen Baker[2,3,47]

[1]International Vaccine Institute, SNU Research Park, 1 Gwanak-ro, 1 Gwanak-gu, Seoul 08826, Republic of Korea. [2]The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, 764 Vo Van Kiet, Quant 5, Ho Chi Minh City, Vietnam. [3]Centre for Tropical Medicine and Global Health, University of Oxford, Old Road campus, Roosevelt Drive, Headington, Oxford OX3 7FZ, UK. [4]Centre for Genomic Pathogen Surveillance, Wellcome Genome Campus, Hinxton, Cambridge CB10 1SA, UK. [5]Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK. [6]Institute of Medical Microbiology, University of Cologne, 50923 Cologne, Germany. [7]Kilimanjaro Christian Medical Centre, P.O. Box 3010 Moshi, Tanzania. [8]Division of Infectious Diseases and International Health, Duke University Medical Center, Durham, NC 27710, USA. [9]Duke Global Health Institute, Duke University, Durham, NC 27708, USA. [10]Centre for International Health, University of Otago, Dunedin 9054, New Zealand. [11]Centers for Disease Control and Prevention, KEMRI Complex, Mbagathi Road off Mbagathi Way, P.O. Box 606-00621 Village Market, Nairobi, Kenya. [12]Emory Global Health Institute, Emory University, 1599 Clifton Road, NE, Atlanta, GA 30322, USA. [13]Kwame Nkrumah University of Science and Technology, P.O. Box PMB KNUST, Kumasi, Ghana. [14]Kumasi Centre for Collaborative Research in Tropical Medicine, Kwame Nkrumah University of Science and Technology, KCCR, UPO, PMB, KNUST, Kumasi, Ghana. [15]University of Antananarivo, BP 566 Antananarivo 101, Madagascar. [16]Institut Supérieur des Sciences de la Population, University of Ouagadougou, 03 B.P. 7118 Ouagadougou 03, Burkina Faso. [17]Armauer Hansen Research Institute, Jimma Road, ALERT Compound P.O. Box 1005 Addis Ababa, Ethiopia. [18]Faculty of Medicine, University of Gezira, P.O. Box 20, Wad Medani, Sudan. [19]Faculty of Science, University of Hafr Al Batin, Al Jamiah, Hafr Albatin 39524, Saudi Arabia. [20]National Institute for Communicable Diseases, Private Bag X4, Sandringham, 2131 Johannesburg, South Africa. [21]Faculty of Health Sciences, University of the Witwatersrand, 1 Jan Smuts Avenue, Braamfontein, 2000 Johannesburg, South Africa. [22]Bernhard Nocht Institute for Tropical Medicine, Bernhard Nocht Str. 74, 20359 Hamburg, Germany. [23]German Center for Infection Research, Hamburg-Borstel-Lübeck, Inhoffenstrabe 7, 38124 Braunschweig, Germany. [24]Institute Pasteur de Dakar, 36 Avenue Pasteur, B.P. 220 Dakar, Senegal. [25]Université Cheikh Anta Diop de Dakar, Dakar B.P. 5005, Senegal. [26]Bandim Health Project, Apartado, 8611004 Bissau codex, Bissau, Guinea-Bissau. [27]Research Center for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen, Denmark. [28]Kenya Medical Research Institute, Mbagathi Rd. P.O. BOX 54840-00200, Nairobi, Kenya. [29]Schiphra Hospital, Ouagadougou 01 01 B.P. 121, Burkina Faso. [30]Institute of Tropical Medicine, Eberhard-Karls University Tübingen, Geschwister-Scholl-Platz, 72074 Tübingen, Germany. [31]Duy Tan University, 254 Nguyen Van Linh, Da Nang, Vietnam. [32]Swiss Tropical and Public Health Institute, University of Basel, Socinstrasse 57, Postfach, CH-4002 Basel, Switzerland. [33]Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St., Baltimore, MD 21205, USA. [34]International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B), GPO Box 128Dhaka 1000, Bangladesh. [35]University of California, Fielding School of Public Health, 650 Charles E. Young Dr. South, Center for Health Sciences, Los Angeles, CA 90095-1772, USA. [36]Medical Research Center (MRC)/Uganda Virus Research Institute (UVRI) & London School of Hygiene and Tropical Medicine (LSHTM) Uganda Research Unit, Plot 51-59 Nakiwogo Road P.O. Box 49Entebbe, Uganda. [37]Uganda Virus Research Institute (UVRI), Plot 51-59 Nakiwogo Road P.O. Box 49Entebbe, Uganda. [38]Public Health Emergency Operations Centre, Plot 6 Lourdel Road, Nakasero PO Box 7272, Kampala, Uganda. [39]Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Atlantic Boulevard, Fajara, P.O. Box 273, Banjul, The Gambia. [40]Murdoch Children's Research Institute, 50 Flemington Road Parkville Victoria, 3052 Melbourne, Australia. [41]Institut de Recherche en Santé, de Surveillance Epidemiologique et de Formations (IRESSEF), Arrondissement 4 Rue 2D1, BP 7325, Dakar, Senegal. [42]Division of Pediatric Infectious Diseases, University of Nebraska Medical Center, 42nd and Emile, Omaha, Nebraska 68198, USA. [43]University of Abuja Teaching Hospital, Gwagwalada, P.M.B 228, Abuja, Nigeria. [44]Bingham University, P.M. B 005, KM 26 Abuja-Keffi Expressway Kodope, Karu, Nasarawa State, Nigeria. [45]Big Data Institute, University of Oxford, Old Road Campus, Oxford OX3 7LF, UK. [46]Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, 30 Flemington Road, Parkville, Victoria 3010, Australia. [47]The Department of Medicine, The University of Cambridge, Box 157, Hills Road, Cambridge CB2 0QQ, UK. These authors contributed equally: Florian Marks, Stephen Baker

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

The Relationship Between Invasive Nontyphoidal *Salmonella* Disease, Other Bacterial Bloodstream Infections, and Malaria in Sub-Saharan Africa

Se Eun Park,[1] Gi Deok Pak,[1] Peter Aaby,[2,3] Yaw Adu-Sarkodie,[4,5] Mohammad Ali,[1,6] Abraham Aseffa,[7] Holly M. Biggs,[8,9] Morten Bjerregaard-Andersen,[2,3] Robert F. Breiman,[10,11] John A. Crump,[8,9,12,13] Ligia Maria Cruz Espinoza,[1] Muna Ahmed Eltayeb,[14] Nagla Gasmelseed,[14] Julian T. Hertz,[8,9] Justin Im,[1] Anna Jaeger,[15] Leon Parfait Kabore,[16] Vera von Kalckreuth,[1] Karen H. Keddy,[17,18] Frank Konings,[1] Ralf Krumkamp,[15] Calman A. MacLennan,[19,20] Christian G. Meyer,[21] Joel M. Montgomery,[10] Aissatou Ahmet Niang,[22] Chelsea Nichols,[1] Beatrice Olack,[23] Ursula Panzner,[1] Jin Kyung Park,[1] Henintsoa Rabezanahary,[24] Raphaël Rakotozandrindrainy,[24] Emmanuel Sampo,[16,25] Nimako Sarpong,[4] Heidi Schütt-Gerowitt,[1,26] Arvinda Sooka,[17] Abdramane Bassiahi Soura,[25] Amy Gassama Sow,[22,27] Adama Tall,[22] Mekonnen Teferi,[7] Biruk Yeshitela,[7] Jürgen May,[15] Thomas F. Wierzba,[1] John D. Clemens,[1,28,29] Stephen Baker,[30] and Florian Marks[1]

[1]International Vaccine Institute, Seoul, Republic of Korea; [2]Bandim Health Project, Bissau, Guinea-Bissau; [3]Research Center for Vitamins and Vaccines, Copenhagen, Denmark; [4]Kumasi Centre for Collaborative Research in Tropical Medicine, and [5]School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [6]Johns Hopkins University, Baltimore, Maryland; [7]Armauer Hansen Research Institute, Addis Ababa, Ethiopia; [8]Division of Infectious Diseases and International Health, Duke University Medical Center, Durham, North Carolina; [9]Kilimanjaro Christian Medical Centre, Moshi, Tanzania; [10]Centers for Disease Control and Prevention, Nairobi, Kenya; [11]Emory Global Health Institute, Emory University, Atlanta, Georgia; [12]Duke Global Health Institute, Duke University, Durham, North Carolina; [13]Centre for International Health, University of Otago, Dunedin, New Zealand; [14]University of Gezira, Wad Medani, Sudan; [15]Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; [16]Schiphra Hospital, Ouagadougou, Burkina Faso; [17]National Institute for Communicable Diseases, and [18]Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [19]Jenner Institute, Nuffield Department of Medicine, University of Oxford, and [20]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom; [21]Institute of Tropical Medicine, Eberhard-Karls University Tübingen, Germany; [22]Institute Pasteur Senegal, Dakar; [23]Kenya Medical Research Institute (KEMRI), Nairobi; [24]University of Antananarivo, Madagascar; [25]Institut Supérieur des Sciences de la Population, University of Ouagadougou, Burkina Faso; [26]Institute of Medical Microbiology, University of Cologne, Germany; [27]Université Cheikh Anta Diop de Dakar, Senegal; [28]International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka; [29]Fielding School of Public Health, University of California, Los Angeles; and [30]Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

Background. Country-specific studies in Africa have indicated that *Plasmodium falciparum* is associated with invasive nontyphoidal *Salmonella* (iNTS) disease. We conducted a multicenter study in 13 sites in Burkina Faso, Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, Sudan, and Tanzania to investigate the relationship between the occurrence of iNTS disease, other systemic bacterial infections, and malaria.

Methods. Febrile patients received a blood culture and a malaria test. Isolated bacteria underwent antimicrobial susceptibility testing, and the association between iNTS disease and malaria was assessed.

Results. A positive correlation between frequency proportions of malaria and iNTS was observed ($P = .01$; $r = 0.70$). Areas with higher burden of malaria exhibited higher odds of iNTS disease compared to other bacterial infections (odds ratio [OR], 4.89; 95% CI, 1.61–14.90; $P = .005$) than areas with lower malaria burden. Malaria parasite positivity was associated with iNTS disease (OR, 2.44; $P = .031$) and gram-positive bacteremias, particularly *Staphylococcus aureus*, exhibited a high proportion of coinfection with *Plasmodium malaria*. *Salmonella* Typhimurium and *Salmonella* Enteritidis were the predominant NTS serovars (53/73; 73%). Both moderate (OR, 6.05; $P = .0001$) and severe (OR, 14.62; $P < .0001$) anemia were associated with iNTS disease.

Conclusions. A positive correlation between iNTS disease and malaria endemicity, and the association between *Plasmodium* parasite positivity and iNTS disease across sub-Saharan Africa, indicates the necessity to consider iNTS as a major cause of febrile illness in malaria-holoendemic areas. Prevention of iNTS disease through iNTS vaccines for areas of high malaria endemicity, targeting high-risk groups for *Plasmodium* parasitic infection, should be considered.

Keywords. *Salmonella*; NTS; invasive NTS; *Plasmodium*; malaria.

Nontyphoidal *Salmonella* (NTS) infections in specific populations in sub-Saharan Africa can result in invasive disease. Invasive NTS (iNTS) disease is associated with diverse, nonspecific clinical features that can be difficult to distinguish from typhoid fever and other febrile illnesses [1, 2]. There is a paucity of data regarding the incidence of iNTS disease in Africa, but a recent systematic review of the global burden of iNTS disease estimated 3.4 million cases in 2010 with the highest burden of disease arising in Africa, with a case fatality rate of 20% [3, 4]. Multiple studies have been conducted to investigate host-associated risk factors for iNTS disease and have identified recent malaria [5], human immunodeficiency virus (HIV) [6], severe anemia [7], severe malnutrition [8], and sickle cell disease [9, 10] to be associated. However, our understanding of the natural history of iNTS, the transmission dynamics of the organisms, the features of asymptomatic human infections, the reservoirs, and the immune responses during infection are incomplete.

Correspondence: S. E. Park, International Vaccine Institute, Kwanak PO Box 14, Seoul, 151-600, Republic of Korea (seeun.park@ivi.int).

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Among the 198 million global cases of malaria in 2013, 584 000 deaths were reported, 90% of which originated from sub-Saharan Africa [11]. The burden of malaria correlates with the force of infection, with disease concentrated among infants and young children in high-transmission areas [12]. Yet, the misdiagnosis of bacteremia as malaria is frequent, especially in sites with inadequate microbiological laboratory infrastructure to identify the pathogenic microorganisms [13]. Where transmission is intense, seemingly healthy older children and adults may experience *Plasmodium falciparum* infection with partial immunity, which may prevent the development of clinical symptoms [14]. This, coupled with the nonspecific clinical presentation of iNTS disease [2], means that patients with iNTS disease may be treated with antimalarials and/or inappropriate antimicrobials. Growing drug-resistant malaria [15] and antimicrobial resistance among iNTS strains implies that empiric antimicrobial regimens may not be effective against the locally circulating organisms [16, 17].

Although the relationship between iNTS disease and malaria has been previously investigated [5, 18], those studies have been constrained by the use of noncomparable study designs and by being restricted to one site. Here we describe the epidemiological features of iNTS disease and malaria in comparison to other community-acquired bacteremias in sub-Saharan Africa using a standardized multicenter approach.

METHODS

Febrile Disease Surveillance

Surveillance of invasive *Salmonella* infections in sub-Saharan Africa was conducted as described elsewhere (Marks F. et al, unpublished data), [19–20]. In brief, standardized healthcare-facility-based surveillance of febrile patients was instituted in 13 sites in sub-Saharan Africa: Nioko and Polesgo, Burkina Faso (BF); Butajira, Ethiopia; Asante Akim North District (AAN), Ghana; Bissau, Guinea-Bissau; the Kibera informal settlement in Nairobi, Kenya; Imerintsiatosika and Isotry, Madagascar; Pikine, Senegal; Pietermaritzburg, South Africa; East Wad Medani (EWM), Sudan; and Moshi Urban and Moshi Rural, Tanzania.

Study Population, Inclusion Criteria, Sample Collection, and Laboratory Diagnoses

Febrile patients from all age groups (except in Ghana, where only children aged <15 years were enrolled) with a tympanic or axillary temperature of ≥38.0°C or ≥37.5°C, respectively, living in the defined study areas were eligible for recruitment. For inpatients, reported fever within the period of 72 hours prior to admission was added to the inclusion criteria (Marks F. et al, unpublished data), [19]. Blood specimens were obtained from febrile patients for aerobic blood culturing (BD Bactec, Becton-Dickinson, Franklin Lakes, New Jersey or BacT/ALERT, bioMérieux, Marcy l'Etoile, France) and malaria diagnostics were performed via a combination of thick and thin blood smears and rapid malaria tests (SD Bioline Malaria Ag P.f/P.v, SD Standard Diagnostics, Suwon, Republic of Korea) that varied among sites.

Data Analysis

As the adjusted incidence rates of bacteremia calculated per 100 000 person-years of observation are described elsewhere (Marks F. et al, unpublished data), here, frequency proportions of bacteremias and *Plasmodium* parasite positivity are presented. After a normality test of our dataset, correlations between malaria and bacteremias from all sites were analyzed with the Spearman correlation coefficient (r). To measure the odds ratios (ORs) of iNTS infections per exposure to malaria endemicity (proportion of malaria frequencies at health facilities used as a proxy), generalized estimating equation (GEE) logistic regression was used. Stratified logistic regression for the univariate and multivariable analysis was performed to understand the individual-level covariates including *Plasmodium spp.* parasite positivity and anemia, considered to be associated with iNTS disease. Data were statistically analyzed taking into account age groups, sex, site-specific characteristics, and clinical data using Microsoft Excel (version 9.0, Microsoft Corporation, Redmond, Washington) and SAS software (version 9.4, SAS Institute, Cary, North Carolina).

RESULTS

Site and Age-Stratified Frequencies of iNTS Disease, Other Bacteremias, Malaria, and Coinfections

A total of 13 431 febrile patients were enrolled and had a blood culture performed during 2010–2014. Of the 13 431 blood cultures, 497 (4%) were positive for a bacterial pathogen: 73 (15%) NTS (*Salmonella* Typhimurium [n = 38/73; 52%], *Salmonella* Enteritidis [n = 15/73; 21%], *Salmonella* Dublin [n = 10/73; 14%], and several other undetermined *Salmonella* serovars [n = 10/73; 14%]); 3 (1%) *Salmonella* Paratyphi A; 137 (28%) *Salmonella* Typhi; and 272 (55%) non-*Salmonella* bacteremias (179/272 [66%] gram-positive and 93/272 [34%] non-*Salmonella* gram-negative bacteremias). The proportion of NTS among positive blood cultures was the highest in Nioko, BF (8/27; 30%) and AAN, Ghana (46/157; 29%), although the proportion of gram-positive bacteremia was equivalently high in the latter (Figure 1).

A total of 11 421 of 13 431 (85%) blood samples were screened for malaria, of which 3133 (27%) were positive by any malaria test. The proportion of malaria frequencies presented at healthcare facilities was the highest in Polesgo, BF (444/744; 60%) and Nioko, BF (430/908; 47%), followed by AAN, Ghana (1139/2651; 43%), and EWM, Sudan (254/632; 40%). Sites in Ethiopia, Madagascar, and Tanzania had the lowest proportion of malaria-positive results. Of 3133 positive malaria tests, 1386 (44%) were from children aged <5 years. All, with the exception of 20 *Plasmodium malariae* and 2 *Plasmodium ovale* infections in AAN, Ghana and with 332 missing data on the *Plasmodium* species, were *P. falciparum* monoinfections.

The proportion of malaria coinfection with any bacterial pathogen from all 13 sites was 11% (53/497), predominantly

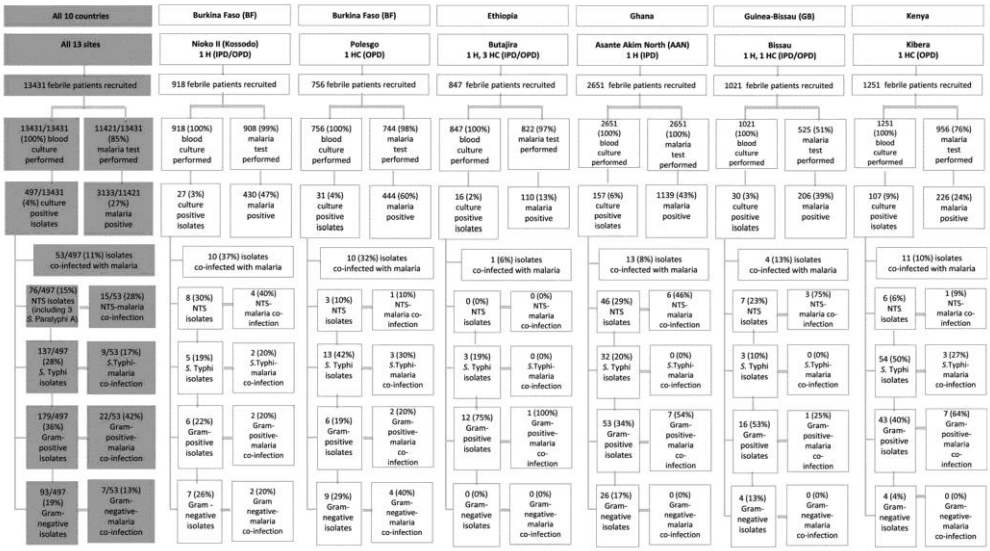

Figure 1. Flowchart of Typhoid Fever Surveillance in Africa Program (TSAP) blood culture and malaria test performance. Blood culture–positive isolates: contaminants excluded (Marks F. et al, unpublished data). Gram-negative isolates: *Salmonella* species excluded. Malaria tests performed per site: Nioko, Burkina Faso (BF; thick/thin blood smears), Polesgo, BF (thick/thin blood smears), Butajira, Ethiopia (Rapid Diagnostic Test [RDT] and thick/thin blood smears), Asante Akim North District (AAN), Ghana (thick/thin blood smears), Bissau, Guinea-Bissau (GB; thick/thin blood smears), Kibera, Kenya (thick blood smear), Imerintsiatosika, Madagascar (MG; RDT and thick/thin blood smears), Isotry, MG (RDT and thick/thin blood smears), Pikine, Senegal (RDT if available and thick/thin blood smears), Pietermaritzburg, South Africa (SA; malaria-free zone: no malaria test performed), East Wad Medani (EWM), Sudan (thick/thin blood smears), Moshi Rural (MR), Tanzania (thick/thin blood smears), and Moshi Urban (MU), Tanzania (thick/thin blood smears). Numerators and denominators for each percentages (%) in the flowchart (in descending order from top to bottom): % of blood culture performed of recruited patients; % of malaria test performed of recruited patients; % of blood culture positive isolates of blood culture performed; % of malaria parasite–positive cases of malaria test performed; % of bacterial isolates

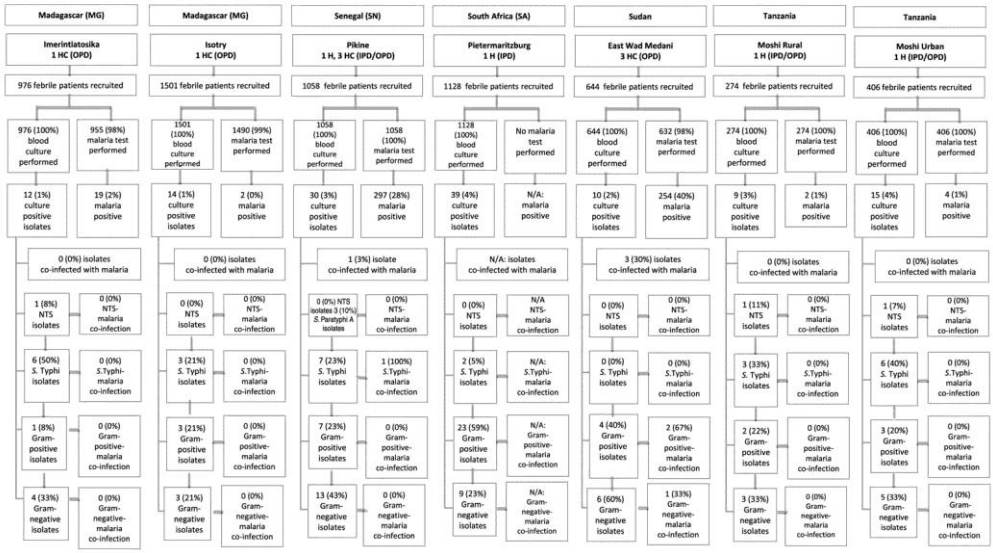

Figure 1 continued. coinfected with malaria of blood culture-confirmed positive isolates; % of nontyphoidal *Salmonella* (NTS), *S.* Typhi, Gram-positive, and non-*Salmonella* gram-negative isolates of blood culture-confirmed positive isolates; % of isolates with NTS-malaria coinfection, *S.* Typhi-malaria coinfection, gram-positive-malaria coinfection, non-*Salmonella* gram-negative-malaria coinfection of all bacterial isolates coinfected with malaria. Malaria species: 2801/3133 malaria positives confirmed with malaria species; 332/3133 missing data on malaria species; 2779/2801 *Plasmodium falciparum*; 20/2801 *Plasmodium malariae*; 2/2801 *Plasmodium ovale*. Malaria species confirmed per site listed below. Nioko, BF: 430/430 *P. falciparum*; Polesgo, BF: 444/444 *P. falciparum*. Butajira, Ethiopia: 26/110 *P. falciparum* and 84 missing data on malaria species. AAN, Ghana: 1111/1139 *P. falciparum*, 20/1139 *P. malariae*, 2/1139 *P. ovale*, and 6 missing data on malaria species. Bissau, GB: 196/206 *P. falciparum* and 10 missing data on malaria species. Kibera, Kenya: not available/226 (no data on malaria species). Imerintsiatosika, MG: 19/19 *P. falciparum*; Isotry, MG: 2/2 *P. falciparum*. Pikine, Senegal: 291/297 *P. falciparum*, and 6 missing data on malaria species. Pietermaritzburg, SA: No malaria test performed as the country is malaria-free. EWM, Sudan: 254/254 *P. falciparum*. MR, Tanzania: 2/2 *P. falciparum*; MU, Tanzania: 4/4 *P. falciparum*. Abbreviations: H, hospital; HC, health center; IPD, inpatient department; NA, not available; OPD, outpatient department.

Table 1. Age-Specific Frequencies of Organisms Isolated From Blood Culture and Malaria Test

Blood Culture–Confirmed Organism	All Ages	0 to <2 y	2 to <5 y	5 to <15 y	≥15 y	Median Age, y (Q1–Q3)
Blood culture performed (No.)	13431	2843	2402	3355	4831	
All pathogenic bacteria (no., % of No.)	497 (4)	126 (4)	107 (4)	141 (4)	123 (3)	5 (1–14)
NTS including 3 *S.* Paratyphi A (no., % of all pathogenic bacteria)[a]	76 (15)	35 (28)	24 (22)	10 (7)	7 (6)	2 (1–3)
Salmonella Typhi (no., % of all pathogenic bacteria)	137 (28)	6 (5)	34 (32)	67 (48)	30 (24)	8 (4–14)
Gram-negative bacteria (no., % of all pathogenic bacteria)[b]	93 (19)	34 (27)	6 (6)	15 (11)	38 (31)	6 (2–14)
Gram-positive bacteria (no., % of all pathogenic bacteria)	179 (36)	50 (40)	42 (39)	47 (33)	40 (33)	4 (1–13)
Malaria test performed (No.)[c]	11421	2136	2031	3007	4247	
Malaria positive (no., % of No.)	3133 (27)	527 (25)	859 (42)	1083 (36)	664 (16)	6 (2–12)
Plasmodium falciparum (no., % of malaria positive)	2779 (89)	500 (95)	782 (91)	913 (84)	584 (88)	5 (2–12)
Plasmodium malariae (no., % of malaria positive)	20 (1)	5 (1)	8 (1)	7 (1)	0 (0)	4 (2–6)
Plasmodium ovale (no., % of malaria positive)	2 (0.1)	0 (0)	0 (0)	2 (0.2)	0 (0)	6 (6–6)
Malarial-bacterial coinfection (no., % of all pathogenic bacteremia)	53 (11)	12 (10)	8 (7)	22 (16)	11 (9)	6 (2–11)
Malaria-NTS (no., % of coinfection)	15 (28)	7 (58)	4 (50)	4 (18)	0 (0)	2 (1–5)
Malaria-*S.* Typhi (no., % of coinfection)	9 (17)	0 (0)	0 (0)	5 (23)	4 (36)	9 (6–22)
Malaria gram-negative (no., % of coinfection)[d]	7 (13)	1 (8)	1 (13)	2 (9)	3 (27)	5 (1–11)
Malaria gram-positive (no., % of coinfection)[e]	22 (42)	4 (33)	3 (38)	11 (50)	4 (36)	7 (3–11)

Abbreviation: NTS, nontyphoidal *Salmonella*.

[a] Total of 3 *S.* Paratyphi A and 73 NTS isolates: 38 of 73 (50%) *Salmonella* Typhimurium, 15 of 73 (20%) *Salmonella* Enteritidis, 10 of 73 (14%) *Salmonella* Dublin, and 10 of 73 (14%) other undetermined *Salmonella* serovars. The 3 *S.* Paratyphi A isolates were all female; 14, 20, and 25 years of age; none exhibited malaria coinfection.

[b] Gram-negative bacteria: *Salmonella* species excluded.

[c] Malaria test was performed through Rapid Diagnostic Test or/and blood film (thick and thin smears) (Figure 1). Of 11 421 blood samples screened for malaria, 3133 (27%) resulted positive: 20 *P. malariae* and 2 *P. ovale* were from Asante Akim North, Ghana. Three hundred thirty-two malaria-positive cases missed data on malaria species. Except for these, all were *P. falciparum*.

[d] Malaria gram-negative coinfection (*Salmonella* species excluded): Of the 7 cases of malaria coinfection with gram-negative bacteria, 3 were *Escherichia coli* (all >15 years of age) and 2 *Pseudomonas aeruginosa* (one <2 years of age, one 5 to <15 years of age). No cases of malaria coinfection with *Klebsiella pneumoniae*.

[e] Malaria gram-positive coinfection: Of 22 cases of malaria coinfection with gram-positive bacteria, 59% (13/22) were *Staphylococcus aureus* (3 between 2 and <5 years, 6 between 5 and <15 years, and 4 aged ≥15 years) and 5 *Streptococcus pneumoniae* (2 under 2 years of age, 3 between 5 and <15 years of age).

gram-positive bacterial coinfection with malaria (22/53; 42%) and NTS-malaria coinfection (15/53; 28%) (Figure 1; Table 1). The malaria/iNTS coinfections were more common among children <5 years of age (11/20; 55%), particularly under 2 years of age (7/12; 58%), whereas all malaria/*Salmonella* Typhi coinfections occurred in children >5 years of age. Children between 5 and 15 years of age had the highest proportion of malaria/bacteremia coinfection with a gram-positive bacterium (11/22; 50%). Children <2 years of age showed the highest proportion of iNTS (35/126; 28% or 35/73; 48%) and gram-positive bacterial infections (50/126; 40% or 50/179; 28%) compared with the other age groups (Table 1).

iNTS–Malaria Correlations, Risk Factors, and Clinical Characteristics

A strong linear correlation of malaria with iNTS across sites was found ($P = .01$; $r = 0.70$) (Figure 2). Areas with higher malaria burden had higher odds of iNTS disease compared with other bacterial infections (OR, 4.89; 95% confidence interval [CI], 1.61–14.90; $P = .005$; GEE logistic regression) than areas with lower burden of malaria (Table 2). Furthermore, relative to non-NTS invasive bacterial infections, *Plasmodium* parasite positivity was associated with iNTS disease (OR, 2.44; 95% CI, 1.09–5.47; $P = .031$; stratified univariate analysis; Table 3).

Patients with severe anemia (hemoglobin level <7 g/dL for age group 0 to <5 years; <8 g/dL for ≥5 years) had >10 times higher odds of iNTS disease (univariate analysis: OR, 13.10; $P < .0001$; multivariable analysis: OR, 14.62; $P < .0001$) than non-NTS bacteremia. Moderate anemia was also associated with iNTS disease (Table 3). Among 76 iNTS patients, which includes 3 *S.* Paratyphi A cases, 34 (45%) had severe anemia and 10 (15%) iNTS patients <10 years of age were severely underweight. iNTS patients exhibited the highest proportion of hospitalizations (54/76; 71%) and diarrhea (22/76; 29%) compared with other bacteremias: 32% (44/137) and 24% (33/137) of patients infected with *Salmonella* Typhi; 54% (96/179) and 16% (29/179) of patients with gram-positive bacterial infections; and 56% (52/93) and 16% (15/93) of patients with non-*Salmonella* gram-negative bacterial infections were hospitalized and had diarrhea.

DISCUSSION

In this study, we demonstrated a positive malaria-iNTS correlation over multiple countries in sub-Saharan Africa. Further, iNTS disease and gram-positive bacteremia were the most common malarial/bacterial coinfections in these areas, exceeding the number of coinfections with *Salmonella* Typhi and non-*Salmonella* gram-negative bacteremia. However, some of the sites (EWM, Sudan and Kibera, Kenya) did not follow this trend, as they had a low level of iNTS infections despite a high burden of malaria. This could be due to low local levels of transmission of iNTS disease, leading to reduced exposure

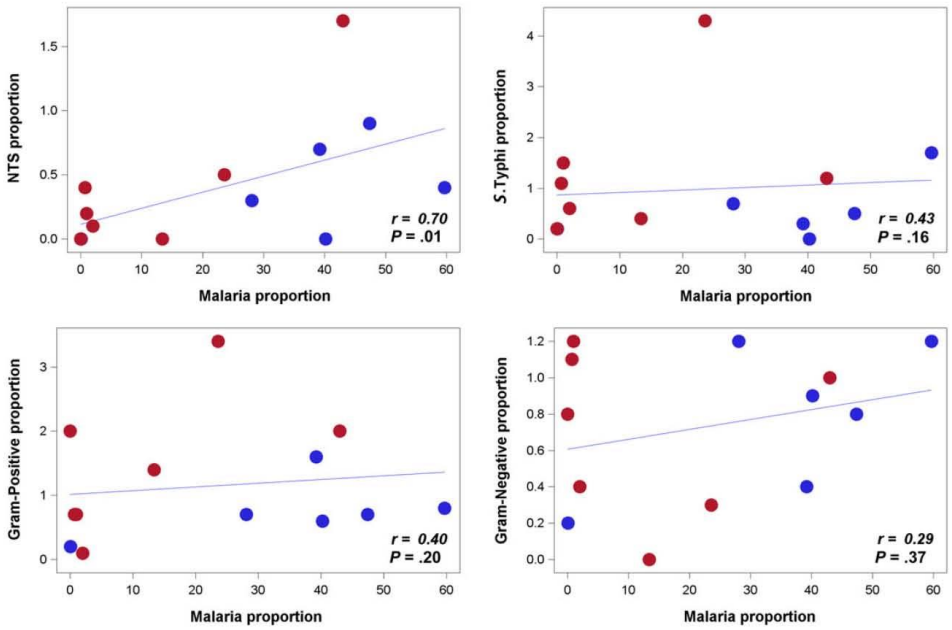

Figure 2. Correlation between frequency proportions of malaria and invasive nontyphoidal *Salmonella* (iNTS) compared to malaria with other invasive bacteria across 13 sites. Spearman correlation coefficient (*r*) is analyzed based on the proportion of frequencies of malaria, iNTS, *Salmonella* Typhi, gram-positive and non-*Salmonella* gram-negative bacterial isolates per site, controlled by each site study period. (Proportions of frequencies are calculated as iNTS, *S.* Typhi, gram-positive bacteria, non-*Salmonella* gram-negative bacteria positivity out of blood culture performed; malaria positivity out of malaria test performed.) Scattered dots represent each study sites. Frequencies of bacteremias and *Plasmodium* parasite positivity per site are noted in Figure 1. Thirteen sites exhibited in the scattered dots are grouped per surveillance period below or above the median duration of surveillance period (20 months). Sites colored in red dots are those with surveillance period of >20 months: Ethiopia, Ghana, Kenya, South Africa, and Tanzania (urban and rural). Sites colored in blue dots are those with a surveillance period of ≤20 months: Burkina Faso (Nioko and Polesgo), Guinea-Bissau, Madagascar (Imerintsiatosika and Isotry), Senegal, and Sudan. Some sites with same or similar values may appear overlapped, but all 13 sites are dotted in the plot. 3 *S.* Paratyphi A isolates from Senegal are grouped under NTS in this analysis.

of children with malaria to iNTS strains. The patterns of iNTS and malaria infections should also be further investigated in the context of the travel history of Kibera residents or rural–urban migration to Kibera, as people residing in Kibera travel within Kenya and their malaria infections may be associated with travel to areas with a greater malaria risk [21].

Our data support other studies [22–24] that suggest an elevated association between iNTS disease and *Plasmodium* parasite–positive individuals. We additionally found a high proportion of gram-positive bacterial coinfections with malaria, contrasting with earlier studies from the Gambia [5] and Malawi [25], that showed a strong association between malaria and iNTS disease, but little evidence for any association between malaria and non-*Salmonella* bacteremias. However, a recent meta-analysis of studies of children with severe malaria and bacteremia [26] indicated that in 5 studies, the overall prevalence of gram-positive organisms in children with malaria was greater than that of gram-negative organisms with *Staphylococcus aureus*, which was the main pathogen isolated in 3 studies. This observation is consistent with malaria-induced impairment of neutrophil function as an underlying causal link: Patients with chronic granulomatous disease, a congenital defect of neutrophil oxidative burst, are particularly susceptible to invasive *S. aureus* and *Salmonella* infections [27].

Although further investigation is required to understand the temporal precedence of infections with malaria parasites and NTS for a risk factor analysis for iNTS disease (including the association between iNTS disease and recent malaria vis-à-vis current malaria or malaria parasite density) [22, 23, 28], a multitude of potential mechanisms may explain this observation. Malaria impairs the oxidative burst function of macrophages and neutrophils, which is likely to increase the risk for iNTS disease, as oxidative burst is key for eliminating *Salmonella* from the intracellular niches [29–32]. More recently, the association has been linked to induction of heme oxygenase-1 (HO-1) in a mouse model of malaria that made mice more susceptible to

Table 2. Characteristics of Bacterial Infection per Malaria Endemicity

Characteristic	Risk Factor (Exposure)			
	Sites With Lower Malaria Endemicity[a] (n[c] = 105)	Sites With Higher Malaria Endemicity[b] (n = 392)	Odds Ratio (95% CI)	*P* Value
iNTS infection[d]	3 (2.9)	73 (18.6)	4.89 (1.61–14.90)	.005
Salmonella Typhi infection	23 (21.9)	114 (29.1)	0.94 (.38–2.32)	.893
Gram-positive bacterial infection	44 (41.9)	135 (34.4)	0.76 (.31–1.84)	.540
Gram-negative bacterial infection	24 (22.9)	69 (17.6)	1.09 (.48–2.46)	.842
Malaria coinfection with all bacteremia[e]	1 (1.5)	52 (14.6)	17.44 (2.76–110.10)	.002

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CI, confidence interval; iNTS, invasive nontyphoidal *Salmonella*.

[a] Sites with lower malaria endemicity (lower-frequency proportions of malaria): Ethiopia (Butajira), Madagascar (Imerintsiatosika, Isotry), Tanzania (Moshi Rural, Moshi Urban), and malaria-free South Africa (Pietermaritzburg) (see Figure 1).

[b] Sites with higher malaria endemicity (higher-frequency proportions of malaria): Burkina Faso (Nioko, Polesgo), Ghana (Asante Akim North District), Guinea-Bissau (Bandim), Kenya (Kibera), Senegal (Pikine), and Sudan (East Wad Medani) (see Figure 1).

[c] No. = blood culture–confirmed real pathogen (excluding contaminants).

[d] iNTS infection: 3 *S.* Paratyphi A isolates grouped under iNTS in this analysis.

[e] Malaria coinfection with all bacteremia is analyzed based on number of blood culture positive cases with malaria test performed. Out of total 497 blood culture positive isolates, 422 had malaria test performed, which is grouped into sites with lower malaria endemicity ($n = 65$) and sites with higher malaria endemicity ($n = 357$).

NTS infection [33]. The same researchers demonstrated that impaired neutrophil oxidative burst was associated with HO-1 induction in Gambian children with malaria [34]. Malaria has also been shown to increase susceptibility to NTS infection in the mice through inhibition of interleukin 12 production [35] and increased interleukin 10 levels [36]. The precise contribution of this HO-1 pathway mechanism to enhanced susceptibility to iNTS disease in humans needs to be further investigated.

The study has some limitations. First, the surveillance period was not long enough to investigate any potential seasonality of malaria, iNTS disease, and coinfections. Second, given that individuals with mild cases of malaria do not necessarily seek healthcare at hospitals, the true burden of malaria is likely to

Table 3. Univariate and Multivariable Analyses of Characteristics Associated With Invasive Nontyphoidal *Salmonella* Disease[a]

Characteristics Associated With iNTS Disease	Univariate Analysis				Multivariable Analysis	
	iNTS (n[b] = 76)	Non-NTS Bacteremias (n[c] = 421)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Malaria parasite positivity	15 (19.7)	38 (9.0)	2.44 (1.09–5.47)	.031	2.10 (.84–5.24)	.110
Nutritional status[d]						
Moderate underweight (<10 y)[e]	8 (11.9)	30 (12.0)	1.05 (.43–2.54)	.917	NA[f]	NA[f]
Severe underweight (<10 y)[g]	10 (14.9)	47 (18.9)	0.96 (.43–2.14)	.919	NA[f]	NA[f]
Anemia status[h]						
Moderate anemia[i]	27 (35.5)	65 (15.4)	6.99 (2.79–17.52)	<.0001	6.05 (2.41–15.21)	.0001
Severe anemia[j]	34 (44.7)	69 (16.4)	13.10 (5.05–33.97)	<.0001	14.62 (5.56–38.43)	<.0001

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CI, confidence interval; iNTS, invasive nontyphoidal *Salmonella*; NA, not applicable; NTS, nontyphoidal *Salmonella*; OR, odds ratio; SD, standard deviation.

[a] Stratified logistic regression was used for this univariate and multivariable analysis.

[b] Total valid case number (n) for iNTS includes the 3 *S.* Paratyphi A cases for this analysis.

[c] Total valid case number (n) for non-NTS bacteremia is the total number of blood culture positives (497) minus total number of NTS isolates (76 including 3 *S.* Paratyphi A): n = 421.

[d] Association between malnutrition (moderate and severe underweight) and iNTS disease compared to non-iNTS bacteremias. Both moderate and severe underweight cases compared with those without malnutrition.

[e] Total valid case number (No.) for moderate underweight cases for patients <10 years of age: NTS (n = 8), non-NTS bacteremia (n = 30). World Health Organization (WHO) Global Database on Child Growth and Malnutrition: *z* score cutoff point of < −2 SD and > −3 SD to classify moderate undernutrition.

[f] Not applicable due to missing data for patients >10 years of age.

[g] Total valid case number (No.) for severe underweight cases for patients <10 years of age: NTS (n = 10), non-NTS bacteremia (n = 47). WHO Global Database on Child Growth and Malnutrition: *z* score cutoff point of < −3 SD to classify severe undernutrition.

[h] Association between anemia (moderate and severe anemia) and iNTS disease compared to non-iNTS bacteremias. Both moderate and severe anemia cases compared with those without anemia.

[i] Moderate anemia: age group 0 to <5 years with hemoglobin level 7–9.9 g/dL, and age group ≥5 years with hemoglobin level 8–10.9 g/dL.

[j] Severe anemia: age group 0 to <5 years with hemoglobin level <7 g/dL, and age group ≥5 years with hemoglobin level <8 g/dL.

be underreported. Different malaria diagnostics may have also influenced the sensitivity and specificity of the results [37], and we were unable to distinguish current from recent malaria in our analysis of iNTS risk factors. Third, HIV testing was not performed, as HIV seroprevalence was not a main objective of the Typhoid Fever Surveillance in Africa Program study. Insufficient clinical data precluded the development of robust diagnostic criteria to better predict the causative agents of the patients and the cause of fever, although diarrhea was indicative of iNTS.

Our standardized multicenter approach adds additional information to the epidemiology of iNTS disease and malaria in Africa. Both the positive correlation between malaria and iNTS disease and the association between malaria positivity and iNTS disease support the role of NTS as a common etiology of invasive bacterial disease among children with malaria in areas where malaria is highly prevalent. Furthermore, given that 2 to several days may be required to confirm bacteremia microbiologically [38], patients with febrile symptoms commonly are given an antimalarial drug and antimicrobials simultaneously, rendering them prone to developing antimicrobial resistance. A similar scenario has occurred with *P. falciparum*, which is already resistant to chloroquine and sulfadoxine-pyrimethamine in most parts of sub-Saharan Africa, and potentially to artemisinin derivatives in the future [15]. A high burden of iNTS disease and malaria, coupled with increasing antimicrobial resistance [39, 40], may potentially contribute to increased severity of illness.

This provides additional evidence to prioritize the development of an iNTS vaccine, specifically designed for the African setting and used in areas of high iNTS prevalence and malaria endemicity. Such a vaccine could either be developed in a single formulation as a bivalent *Salmonella* Typhimurium and *Salmonella* Enteritidis regimen, given their predominance in sub-Saharan Africa as also found in our study, or as a trivalent compound, including *Salmonella* Typhi. Irrespective, surveillance for bacterial bloodstream infections to identify prevalent isolates should continue to monitor emerging pathogens and antimicrobial resistance. Further research on the development of rapid and accurate diagnostics of invasive *Salmonella* infections to minimize the risk of unnecessary simultaneous exposure to both antibiotics and antimalarials for those febrile patients is also warranted.

Notes

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