

# Typhoidal and non-typhoidal *Salmonella* infections in Africa

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**Abstract** *Salmonella* infections in humans can range from self-limiting gastroenteritis typically associated with non-typhoidal *Salmonella* (NTS) to typhoidal fever, which can be life-threatening. Salmonellosis causes considerable morbidity and mortality in both humans and animals, and has a significant socioeconomic impact worldwide. In Africa, it is difficult to evaluate the situation of salmonellosis due to the non-availability of facilities capable of performing the tests essential for the diagnosis of typhoidal and non-typhoidal *Salmonella* infections. This article reviews important work in the literature, including the epidemiology, disease burden, pathogenesis, genomics, diagnosis, treatment, emergence and tracking of multidrug-resistant (MDR) *Salmonella* infections and intercontinental transmission of *Salmonella* to Africa. Searches of PubMed and Google Scholar were completed and the retrieved list of relevant publications were further screened. The literature revealed that the most common form of the disease in Africa is gastroenteritis, with bacterial multiplication in intestinal submucosa and diarrhoea caused by the inflammatory response and, perhaps, also by toxins. In addi-

tion to the high burden of *Salmonella* infection in Africa, MDR *Salmonella* species is on the rise in the continent, which might pose difficulties in the treatment of the disease.

## Introduction

*Salmonella* are members of the Enterobacteriaceae, facultatively anaerobic Gram-negative bacilli able to grow on a wide range of relatively simple media and distinguished from other members of the family by their biochemical characteristics and antigenic structure [1]. The genus *Salmonella* consists of only two major species: *Salmonella enterica* and *Salmonella bongori*. *Salmonella enterica* is divided into six subspecies, which are distinguished by certain biochemical characteristics and susceptibility to lysis by bacteriophage Felix 01 [2]. *Salmonella enterica* is divided into seven phylogenetic groups, subspecies I, II, IIIa, IIIb, IV and VII. Subspecies I includes 1367 serovars, some of which are commonly isolated from infected birds and mammals, including humans. The other subspecies mainly colonise cold-blooded vertebrates [3]. According to Su and Chiu [4], in 2005, all *Salmonella* species became officially recognised as a single species, *S. enterica*, based on their close relationship by DNA hybridisation studies. In the past, *Salmonella* had been named based on the original places of isolation, such as *Salmonella london* and *Salmonella indiana*. This system was replaced by the classification based on the susceptibility of isolates to different selected bacteriophages, which is also known as phage typing [5]. Phage typing has proved extremely useful for discriminating within strains of *Salmonella typhimurium*, *virchow*, *enteritidis* and *typhi* [1]. *Salmonella* serotypes can, however, be broadly grouped into typhoidal and non-typhoidal *Salmonella*, depending on the clinical syndrome associated with them [6].

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*Salmonella* infections are of public health significance worldwide, particularly with regards to developing countries, where they are a leading cause of morbidity and mortality [7]. They cause a variety of infectious diseases in both humans and animals. The most common of such disease is gastroenteritis, with bacterial multiplication in intestinal submucosa and diarrhoea caused by the inflammatory response and, perhaps, also by toxins [3]. Infections caused by *Salmonella* have been categorised into four clinical types: gastroenteritis, bacteraemia or septicaemia, enteric fever and convalescent lifetime carrier state.

### Kauffman–White classification

The Kauffman–White classification scheme is a system employed in the classification of *Salmonella* into serotypes taking cognizance of their surface antigens, the O (somatic) and H (flagella) antigens. The somatic antigens are the side chains of repeating sugar units projecting outwards from the lipopolysaccharide layer on the surface of the bacterial cell wall, while the flagella antigens are formed from structural proteins which make up the flagella. *Salmonella* exhibits two distinct H antigens: phases 1 and 2. An example of an antigenic formula for the serovar *S. typhimurium* according to the Kauffman–White scheme is 1,4,5, 12:i:1,2, where 1, 4, 5 and 12 are O antigen, i is phase 1 H antigen and 1 and 2 are phase 2 H antigen [8].

### Non-typhoidal *Salmonella*: prevalence in Africa

Non-typhoidal *Salmonella* (NTS) has a worldwide occurrence. In developed countries, it is associated with mild gastrointestinal illness, which is usually self-limiting and antimicrobial treatment is not recommended [9]. In Africa, NTS infections appear to be endemic, being one of the major causes of bacteraemia, mostly in children, with 4100 deaths per year [10]. This is more prevalent in areas where malaria, malnutrition and HIV are high. Mandomando et al. [11, 12] reported a high burden of invasive NTS (*S. typhimurium* and *S. enteritidis*) infection among young children in Mozambique. Feasey et al. [13] also reported 32 % compared with 54 % of invasive NTS in children <15 years of age in South Africa and Malawi, respectively. In a similar study, Bahwere et al. [14] reported *Salmonella* spp. as a cause of 73 % of cases of bacteraemia in children in rural Central Africa. In Mali, three serovars *S. typhimurium*, *S. enteritidis* and *S. dublin*, accounted for the majority of NTS isolated from infants and young children [15]. In Côte d'Ivoire, the mortality rate was estimated to reach 5 % from *Salmonella* infections. From studies carried out between 2005 and 2009 among isolated serotypes, NTS were prevalent. Typing was possible

for 76.1 % of strains, of which 37 % was *S. typhimurium* and 16 % was *S. enteritidis* [16]. Mohamed and Suelam [17] identified a high incidence rate (13.3 %) of *Salmonella* infections in human diarrhoeic cases examined in Egypt. It was found out that all serotypes ( $n = 4$ ) isolated from human stool samples were *S. enteritidis*. NTS isolates from paediatric cases in Kenya revealed a majority to be *S. typhimurium* (106 out of 193, 54.9 %) and *S. enteritidis* (64, 33.2 %) [9]. Labi et al. [18] reported a 6.5 % ( $n = 181/2768$ ) prevalence of *Salmonella* bacteraemia at the Korle-Bu Teaching Hospital in Ghana, with a preponderance of NTS over typhoidal *Salmonella*. Children under 5 years old bore the brunt of the disease. Though there has been a high prevalence of NTS in Africa, infection in some cases might be self-limiting in relatively healthy individuals. This was attributed to the infection subsiding on its own and also the possibility of intake of self-prescribed antibiotics. In a related study by Ifeanyi et al. [19], only NTS were isolated from children under 5 years old presenting with gastroenteritis in Abuja, Nigeria. The isolates were *Salmonella zanzibar*, *Salmonella brancaster* and *S. enteritidis*.

Another report from Nigeria by Abdullahi et al. [20] showed that, of a total of 108 *Salmonella* isolates from both blood and stool samples, 43.5 % were NTS while 56.5 % were typhoidal salmonellosis amongst both adults and children.

### Clinical manifestation of NTS

NTS usually causes self-limiting gastroenteritis associated with nausea, abdominal pain, vomiting and inflammatory diarrhoea. In some cases, specific strains among the serovars can cause bacteraemia majorly in young children and immunocompromised patients. Incubation of NTS after ingestion of the pathogen is between 6 and 12 h [21, 22].

### Emergence of antibiotic-resistant non-typhoidal *Salmonella* in Africa

Antibiotic-resistant NTS is becoming a major public health concern in Africa, as data from studies indicate an increase in the emergence of antibiotic-resistant strains. There have been reports of multidrug-resistant (MDR) *S. typhimurium* and *S. enteritidis* in several African countries. Mandomando et al. [11] reported a high occurrence of *S. typhimurium* and *S. enteritidis* resistant to ampicillin, chloramphenicol and trimethoprim–sulphamethoxazole in Mozambique. This is similar to the report of Oundo et al. [23], whose work revealed that 35 % of NTS isolates were resistant to ampicillin, 18 % were resistant to chloramphenicol and 39 % were resistant to sulphamethoxazole–trimethoprim in Kenya. Mengistu et al. [24] reported that more than 37 % of *Salmonella* serovars were resistant to ampicillin, tetracycline and co-trimoxazole

in Ethiopia. In Nigeria, Abdullahi et al. [20] reported high resistance to ampicillin (94.2 %), chloramphenicol (72.8 %) and lower resistance (31.8 %) to co-trimoxazole. The NTS isolated by Ifeanyi et al. [19] were resistant to amoxicillin and cefuroxime (55.5 % each). In South-Western Nigeria, Olowe et al. [25] reported a 91.3 % resistance rate for amoxicillin and co-trimoxazole, 86.9 % for ampicillin, 82.6 % for streptomycin and 30.4 % for ciprofloxacin (Table 1). Interestingly, none of the NTS from these studies in Nigeria were resistant to ciprofloxacin, nalidixic acid or ofloxacin. Most studies in Africa have reported NTS susceptibility to fluoroquinolones [27]. Akinyemi et al. [26] isolated *Salmonella* serotypes that had reduced susceptibility to fluoroquinolones in Nigeria. This is a new scourge which was also reported by Boni-Cissé et al. [16] and Lunguya et al. [28] in Côte d'Ivoire and the Democratic Republic of Congo, respectively. In Côte d'Ivoire, resistance to nalidixic acid was 38 % and reduced susceptibility to ciprofloxacin was 14 %, while in the Democratic Republic of Congo, there was 15.4 % decreased susceptibility to ciprofloxacin. However, one study from northern Nigeria reported 100 % resistance of human NTS to fluoroquinolones [29]. There are some documented underlying conditions that may have contributed to such failure, which include diabetes, AIDS, chronic liver disease, aortic aneurysm surgery and spherocytosis [30]. In comparison with data from other continents of NTS serovars resistant to ciprofloxacin, Africa is second only to Asia [31]. Investigation conducted so far suggest that an alteration in *gyrA* is solely responsible for resistance [32]. This is attributed to a point mutation in the quinolone resistance determining region (QRDR) of the topoisomerase gene *gyrA*. However, in Lagos, Nigeria, it was observed that MDR NTS isolated from HIV patients was chromosomally mediated [33].

### Transmission of non-typhoidal *Salmonella*

The transmission of NTS in Africa has not been well established. However, there has been speculation of human-to-human transmission coupled with food-borne transmission, which is said to be the predominant source of transmission [9, 34]. Kagambèga et al. [35], in their study, carried out a comparison of NTS isolated from the faeces of cattle, poultry, swine and hedgehogs to NTS isolated from humans in Burkina Faso. It was observed that *S. typhimurium* isolates from poultry and humans were multi-resistant to the same set of antimicrobials (ampicillin, chloramphenicol, streptomycin, sulphonamides and trimethoprim). Also, they had the same phage type DT56 and were closely related in pulsed-field gel electrophoresis (PFGE). Furthermore, *S. muenster* isolated from hedgehogs had similar PFGE patterns as the domestic animals, which implies that domestically produced animals and wild animals can share the same *Salmonella*

**Table 1** Reported percentage antibiotic resistance of non-typhoidal *Salmonella* in Nigeria

Antibiotics	% resistance	Year(s)	Reference(s)
Amoxicillin	91.3, 55.6	2007, 2014	[19, 25]
Ampicillin	86.9, 94.2	2007, 2014	[20, 25]
Cefuroxime	55.5	2014	[19]
Cephalexin	55.6	2014	[19]
Co-trimoxazole	91.3, 31.8	2007, 2014	[20, 25]
Nalidixic acid	4.9	2014	[20]
Amoxicillin–clavulanic acid	22.2	2014	[19]
Chloramphenicol	72.8	2014	[20]
Streptomycin	82.6	2007	[25]
Ciprofloxacin	14.8, 30.4	2000, 2007	[25, 26]

serotypes and potentially transmit some of them to humans. A similar study in Tunisia suggested the possibility of circulating epidemic strains between contaminated animal-derived meat and humans [36]. Several risk factors have, over time, been identified as factors that can foster the transmission of NTS, which include environment (food and water, hospital-acquired infection, direct and indirect animal contact, transmission between humans) and host (age, HIV infection, malnutrition, sickle cell disease, malarial anaemia, schistosomiasis and recent antimicrobial use) [37].

### Tracking the transmission of emerging multidrug-resistant *Salmonella* serovars

With the application of recent sequencing technologies, tracking of the emergence and transmission of MDR *Salmonella* serovars has been made possible. Both MDR typhoidal and non-typhoidal *Salmonella* serovars can be tracked using whole-genome DNA sequencing. Multilocus sequencing analysis of invasive *S. typhimurium* from Malawi and Kenya identified a dominant type, designated ST313, which was rarely reported outside of Africa [38]. Whole-genome DNA sequences have revealed that the worldwide *S. typhi* population is highly clonal and probably originated from a common ancestor that moved into the human population several thousand years ago. Phylogeographical analysis of the dominant MDR H58 clade of *S. typhi* revealed an intercontinental (Asia–East Africa) and intracontinental (East–South Africa) transmission [39].

### Difference between typhoidal and non-typhoidal *Salmonella*

With over 2600 different serovars, *S. enterica* is greatly diverse, hence the need to know the difference between

typhoidal and non-typhoidal *Salmonella*, as both are of the same species but result in different disease manifestation. *Salmonella typhimurium* and *S. enteritidis* have a wide host specificity compared to typhoidal strains that are human host-specific. In terms of epidemiology, NTS has a global burden in contrast to typhoidal *Salmonella*, which is majorly endemic in developing countries, such as South-East Asia and Africa. This could be attributed to poor sanitary environment and low standard of living. Also, there are no human vaccines available for NTS, while killed whole-cell parenteral vaccine, live-attenuated oral vaccine and Vi polysaccharide capsule-based vaccine are available [22].

## Typhoid fever in Africa

### Epidemiology

Enteric fever (typhoid and paratyphoid fevers) is a febrile illness caused by *S. typhi* and *Salmonella paratyphi* A, B and C [40]. Worldwide, typhoid fever is an important cause of morbidity and mortality, with an estimated 16–33 million cases and 500,000–600,000 deaths annually [41]. *Salmonella typhi* is endemic in developing countries such as Africa, in contrast to developed countries, where the incidence is much lower and the majority of cases occur among travellers returning from endemic areas [42]. In 2002, it was estimated that a total of 408,837 cases occurred in Africa [43]. However, the exact distribution of typhoid fever in Africa is not well documented due to the non-availability of facilities capable of performing the blood culture tests essential for the diagnosis of typhoid fever and, also, typhoid fever is commonly attributed to malaria [44, 45].

Typhoid fever is transmitted through the faecal–oral route via contaminated water and food. It is prevalent among impoverished populations [46] that are overcrowded, with poor access to sanitation and are exposed to unsafe water and food, and also affects travellers bound to endemic countries [47]. Food handlers also play a prominent role in the transmission of typhoid fever [48]. Typical symptoms of enteric fever include fever, chills, hepatosplenomegaly and abdominal pain. In addition, patients may experience nausea, rash, diarrhoea or constipation and headaches [49].

### Estimates of typhoid fever disease burden in Africa

Knowledge of the burden of disease is vital in order to know the effects of the disease on human health. Hence, efforts to understand the trend of typhoid fever in Africa require the need for well-planned studies. In Egypt, a study [50] was carried out to determine the population-based incidence of typhoid fever and, of 1815 patients evaluated, cultures yielded 90 (5 %) *S. typhi* isolates and the estimated incidence of

typhoid fever was 59/100,000 persons/year. Studies on typhoid infection from Egypt are in the medium incidence range, but a study from South Africa reported a high incidence range for the South African region [43].

In Ghana, it was reported that typhoid fever was among the leading causes of outpatient illness, accounting for 0.92 % of hospital admissions [51]. Also, in Ghana, typhoid fever incidences were calculated for the period from September 2007 to November 2008, and 2.5 % of the isolates were positive for *S. typhi*. The frequency of typhoid fever was low among children <2 years of age (0.7 %), while among those children between 2 to <11 years of age it was 7.0 % and among children  $\geq$ 11 years of age it was 4.6 % [52]. In Kenya, a study by Breiman et al. [53] reported very high rates of bacteraemic typhoid fever in urban areas in Kenya (247/100,000 per population per year). In Nigeria, a study of a 4-year cumulative prevalence of *Salmonella* infection in Akwa Ibom state using hospital-based data reported a high prevalence (63.8 %) of typhoid fever in both sexes and all age groups [54]. A study from Northwest Nigeria showed *S. typhi* to be the most frequently encountered, in 40.7 % of cases [20]. A study in Tanzania reviewed typhoid records for 5 years, with the results indicating that there was a fluctuating trend of typhoid occurrence, and the overall typhoid fever prevalence between 2003 and 2007 indicated an increasing trend from 771 to 942 cases/100,000 persons [55]. In Cameroon, a cross-sectional study was carried out to determine the prevalence of typhoid fever in 200 patients and typhoid fever was confirmed in 2.5 % [56].

### The bacterium

*Salmonella typhi* belongs to the family Enterobacteriaceae of the general group of enteric bacteria that includes *Escherichia coli* and *Shigella* species [57]. It is a Gram-negative bacillus which is aerobic and facultative anaerobic. Serologically, *S. typhi* is positive to lipopolysaccharide antigen 09, 12, protein flagellar antigen Hd and capsular polysaccharide antigen Vi [46]. *Salmonella typhi* is human host-restricted; thus, humans are the only known natural host of *S. typhi* [58] and study has shown that isolates of *S. typhi* are highly clonally related [59].

### Genomics of *S. typhi*

The genome of *S. typhi* consists of approximately 5 million base pairs (bp) encoding about 4000 genes, of which more than 200 are pseudogenes [57, 60]. A remarkable characteristic of the *S. typhi* genome is the presence of the pseudogenes and more than half of which are inactivated by the introduction of a stop codon. A significant number are predicted to be involved in housekeeping functions, virulence or host

interactions, and this inactivation of genes which is responsible for host interactions may explain why *S. typhi* is human host-restricted [46].

The complete DNA sequences of two different *S. typhi* isolates include the *S. typhi* type strain Ty2 originally isolated in the early 1900s and *S. typhi* CT18, an MDR strain which was isolated in 1993 from a child with typhoid fever in the Mekong Delta region of Vietnam [57–59]. *Salmonella typhi* Ty2 was the basis for vaccine development and was the parent of mutant strains Ty21a and CVD908, which were used in trials of live-attenuated vaccines and contains no plasmids [58]. However, *S. typhi* CT18 with a total size of 4,809,037 bp is an example of an MDR microorganism [59]. *Salmonella typhi* CT18 contains two plasmids and the larger conjugative plasmid, pHCM1, is 218 kb in length and encodes resistance to chloramphenicol, ampicillin, trimethoprim, sulphonamides and streptomycin. The smaller plasmid, pHCM2, is 106.5 kb in length and is phenotypically cryptic [46, 57].

Also, Vi polysaccharide capsule production is one of the major characteristics of most *S. typhi* isolates and is associated with a set of genes that are situated within a gene island of 134 kb that encodes a variety of putative virulence-associated gene clusters (including the Vi) known as SPI-7 [61].

### Pathogenesis and pathology of typhoid fever

Upon the ingestion of *S. typhi* in contaminated food or water by the host, it passes through the stomach and invades the gut epithelium of the human host. *Salmonella typhi* enters the host's system primarily through the distal ileum and is transported into the lymphatic system [62]. Attachment promoted by the bacterium may be necessary before invasion can occur and *S. typhi* has specialised fimbriae that adhere to the epithelium in the ileum (Peyer's patches). Once there, they pause and continue to multiply until some critical point is attained. The critical point is most likely determined by the number of bacteria, their virulence and the host response [46]. The incubation period is usually 7 to 14 days, after which the bacteria break out into the bloodstream to invade the rest of the body. Bacteria that do not re-infect the host are naturally shed in the stool and are then ready to infect other hosts [46]. Once *S. typhi* invades the gut epithelium, it encounters macrophages within the gut-associated lymphoid tissue. Hence, the interaction between *Salmonella* and macrophages lead to an alteration in the expression of a number of host genes, such as those encoding pro-inflammatory cytokines (including IL-1, IL-6, IL-8, TNF- $\beta$ , INF, GM-CSF), receptors, adhesion molecules and anti-inflammatory mediators, as well as those involved in cell death or apoptosis [62, 63].

The Vi-positive strains of *S. typhi* are more infectious and highly virulent compared to Vi-negative strains [46]. The initial interaction between *S. typhi* and the human gut is less

inflammatory due to the absence of neutrophilic intestinal infiltrates in the acute phase of typhoid fever, which suggests a tendency for typhoidal *Salmonella* to evade aspects of the innate immune response and cause a systemic infection [64].

Pathology in the Payer's patches include hyperplasia of lymphoid follicles, necrosis of lymphoid follicles and ulceration in the long axis of the bowel, with the possibility of perforation and haemorrhage [63].

### Virulence factors of *Salmonella* species

Several *Salmonella* virulence mechanisms have been identified to describe the disease presentation, including altered flagellin gene regulation [65], altered invasion gene regulation [66], expression of the typhoid toxin [67] and expression of the virulence-associated (Vi) capsular polysaccharide [68]. *Salmonella* pathogenicity islands (SPIs) are responsible for the majority of the virulence factors of the bacterium [69]. The ability of *Salmonella* to survive and replicate within the phagosome is mediated by *Salmonella* pathogenicity island 2 (SPI-2), which inhibits movement of reactive oxygen intermediates and reactive nitrogen intermediates into the phagosome [70]. However, SPI-7 is the most significant pathogenicity island in *S. typhi* infection because it codes for the Vi antigen that is expressed on the cell surface. The Vi antigen is essential for increased virulence and severity of symptoms [71].

Most of the effector molecules associated with the pathogen's virulence are encoded on the SPIs. The type III secretion system (T3SS) proteins encoded by two SPIs are linked with the pathogenicity at the molecular level. The T3SS structural genes positioned on SPI-1 include *prgHIJK*, *spaMNOPQRS* and *invABCEFGH*, as well as multiple regulatory and effector genes [69, 72]. *Salmonella typhi* secretes effector proteins which include, SipA, SipB, SipC, SopA, SopB, SopC, SopD, SopE, SptP, SpiC and SseF. SipA and SptP alter the actin cytoskeleton of the host cell, which is responsible for cell migration [69, 73]. Recently, Smith et al. [74] from Lagos, Nigeria reported 73 out of 76 isolates (96.1 %) to be positive for the *invA*, gene while 38 (50 %) possessed the *sitC* gene out of the 76 isolates tested. Therefore, they recommended the use of the *invA* gene for *Salmonella* detection in food samples in Nigeria. In a study by Adesiji et al. [75] on 16 NTS clinical isolates from north central Nigeria, all found to harbour the *invA* gene, while a study by Dione et al. [76] from Gambia tested 185 NTS for the presence of 12 virulence genes and found the genes present in at least 70 % of the isolates. Karmi [77] from Egypt reported on all NTS isolates from poultry and meat samples positive for the *invA* gene.

### Host immune response to *S. typhi*

During invasive *Salmonella* infection, *Salmonella* pathogen-associated molecular patterns (PAMPs) and danger-associated

molecular patterns (DAMPs) initiate the innate immune system, leading to activation and recruitment of neutrophils, dendritic cells (DCs), inflammatory monocytes and macrophages, and the production of pro-inflammatory cytokines, most notably IL-1, IL-2, IL-6 and IL-8, tumour necrosis factor (TNF)- $\alpha$ , and interferon (IFN)- $\gamma$  [78]. Also, *S. typhi*-infected macrophages can be stimulated by producing lysosomal enzymes, reactive nitrogen intermediates, reactive oxygen intermediates and other antimicrobial peptides in order to destroy or limit the replication of *Salmonella* [79].

Clearance of *S. typhi* from tissues requires the CD28-dependent activation of CD4+, T cell receptor (TCR)- $\alpha$   $\beta$  T cells and is controlled by major histocompatibility complex (MHC) class II genes. DCs antigen-presenting cells process the antigen and present it on MHC class II molecules to naive T cells [72].

### Diagnosis of *S. typhi*

*Salmonella typhi* or *S. paratyphi* can be detected either by culture of the organism or by the serological methods using serum or urine samples. The organism may be cultured from blood, bone marrow, stool or urine [63]. The gold standard method for confirming typhoid fever is an isolation of *S. typhi* from bone marrow and this requires equipment and trained laboratory personnel. However, they are not available in primary healthcare facilities and hospitals in the developing world [80]. In 2011, Keddy et al. [81] evaluated three diagnostic methods for detecting antibodies to *S. typhi* and used blood culture as the standard for comparison. Patients were recruited for the study from two sub-Saharan African sites [81]. It was reported that all typhoid rapid antibody tests performed poorly compared with blood culture and it was concluded that such tests may be useful only during emergencies such as outbreaks and was not recommended for routine care settings in sub-Saharan Africa. However, Smith et al. [82] recommended the use of both *S. typhi* culture from faecal samples and the Widal test for diagnosis. In Africa, the most common diagnosis of *S. typhi* is serological Widal's test [83] and typhoid fever in most developing countries is a disease of over- and under-diagnosis [84]. Rapid tests used in the diagnosis of typhoid fever include Typhidot, TUBEX and Multi-Test Dip-S-Ticks to detect immunoglobulin G (IgG) and IgM, (IgM) and IgG, respectively. Olsen et al. [85] reported the sensitivity and specificity of these kits to be 89 and 53 % for Multi-Test Dip-S-Ticks, 79 and 89 % for Typhidot, 78 and 89 % for TUBEX, and 64 and 76 % for Widal testing in hospital findings. Also, Ismail [86] reported the evaluation of Typhidot specificity and sensitivity to be 75 and 95 %, respectively, in clinical settings. In addition, Krishna et al. [87] reported in a previous study that the Typhidot (IgM) test is a reliable and rapid test for the diagnosis of typhoid fever, with a sensitivity of 100 % and a specificity of 95.5 %. This is

in consonance with the report of Smith et al. [88], which revealed 97.8 % specificity. Recently, a systematic review on the diagnosis of typhoid fever was performed by Storey et al. [89] and it was reported that blood culture (70 %) was the most frequently used test, while the Widal test accounted for only 7 %. This implies that the Widal test is not a method of assay in other clans except Africa. However, they recommended the approval of a composite reference standard to detect typhoid fever which can enhance the estimation of diagnostic validity.

### Culture

The liquid and solid media that are suitable for the isolation of *S. typhi* and salmonellosis include strontium selenite broth, which is better than selenite F broth for the isolation of *S. typhi*; *Salmonella–Shigella* agar has been found to work better than xylose–lysine deoxycholate agar and modified bismuth sulphate agar, which is better than deoxycholate agar for the growth of *Salmonella* spp. The organism is less frequently isolated from urine, and culture of bone marrow may yield more isolates of the organism even when it cannot be obtained from blood, stool or urine [63].

### Serological tests

The Widal test, which measures the antibody titres to the O (somatic) and H (flagella) antigens, is relied upon widely in Africa, although serological tests are of little value because they are neither sensitive nor specific and are not confirmed suitably for widespread adoption. An enzyme immunoassay for the rapid detection of *S. typhi*-specific IgM and IgG antibodies has been reported to be sensitive but has not been confirmed for widespread implementation. Smith et al. [88] employed the classical Widal test and rapid latex agglutination assay for typhoid fever diagnosis. In comparison, the simple and rapid test was more sensitive to the Widal test. The classification for the genus *Salmonella* by Kauffman was recognised on the basis of the serologic identification of O (somatic), which forms the immunodominant part of LPS and H (flagellar) antigens, the filamentous portion of the bacterial flagellum. Each serotype was considered a separate species based on the Kauffman–White scheme [90].

### Antimicrobial resistance of *S. typhi*

Antimicrobial resistance in developing countries is a major public health problem and the emergence of *S. typhi* MDR strains has been the main challenge to healthcare systems and is, therefore, of major concern [42], whereby the effective treatment for the disease is reduced, leading to complications and death. Multidrug resistance to the traditional first-line antimicrobial agents ampicillin, chloramphenicol and

trimethoprim–sulphamethoxazole is common among *S. typhi* [91, 92] and MDR strains resistance to ampicillin, chloramphenicol and trimethoprim has been encoded by plasmids belonging to the H1 incompatibility group (incH1) [42]. In Africa, antimicrobial susceptibility data are insufficient and this issue is challenging and of great concern, since treatment with proper antimicrobial drugs is essential for the effective treatment of *S. typhi*. In Nigeria, it was reported in a study that *S. typhi* strains were resistant to at least three antibiotics, giving a prevalence of 80.7 % [93, 94], i.e. a high prevalence of MDR *S. typhi*. Also, Akinyemi et al. [95] confirmed the circulation of multidrug resistance in *S. typhi* isolated from patients with typhoid fever complications in Lagos, Nigeria. In Ghana, Mills-Robertson et al. [96] reported multidrug resistance in 30 of 58 isolates based on their resistance to three out of the five antibiotics tested. MDR *S. typhi* was also reported in a study by Lunguya et al. [28] in the Democratic Republic of Congo, in Togo [97] and on the Malawi–Mozambique border [98].

The emergence of MDR strains that were resistant to the first-line antimicrobial drugs was made known in the 1980s, after which strains resistant to fluoroquinolones emerged in the 1990s [99]. Resistance to nalidixic acid (minimum inhibitory concentration > 256 mg/l) serves as a marker for the detection of reduced susceptibility of *Salmonella* spp. to fluoroquinolones. Resistance to fluoroquinolones in *S. typhi* has been linked to be mediated by chromosomal mutations, in the target proteins, DNA gyrase, encoded by *gyrA* and *gyrB* or by plasmid-mediated resistance [100] and antimicrobial resistance, notably to fluoroquinolones, is on the increase [101]. Fluoroquinolones act by inhibiting the topoisomerase enzymes, DNA gyrase and topoisomerase IV, and a number of resistance mechanisms have been documented, such as point mutations that result in amino acid substitutions in the topoisomerases, reduced outer membrane permeability, increased efflux of antibiotics and the plasmid-encoded Qnr genes [101]. In Africa, Keddy et al. [102] reported fluoroquinolone-resistant typhoid fever in South Africa. Also, Kariuki et al. [44] reported the trends in resistance to quinolones and the distribution of drug resistance phenotypes among *S. typhi* isolates from three surveillance periods.

### Multidrug-resistant *S. typhi* H58 clone

The MDR *S. typhi* H58 clone has become prevalent in the Indian subcontinent, South-East Asia and has also spread to Eastern Africa. This clone acquired a large conjugative incH1 pST6 plasmid encoding resistance to co-trimoxazole, ampicillin and chloramphenicol. MDR *S. typhi* showed reduced susceptibility to ciprofloxacin and also turned out to be resistant to quinolones as far back as the 1990s [103]. In Africa, Feasey et al. [104] and Kariuki et al. [44] reported an increase in the

incidence of the MDR H58 lineage of *S. typhi* in Blantyre, Malawi, and H58 multidrug resistance in Kenya, respectively.

### Vaccination

Currently, typhoid fever can be treated with antibiotic drugs, but the alarming rates of antibiotic resistance calls for vaccination in high-risk populations with typhoid fever [105]. Hence, the World Health Organization (WHO) recommends the use of two licensed vaccines, Ty21a and Vi [105]. Ty21a is an oral live-attenuated vaccine and Vi is an injectable capsular polysaccharide vaccine. Both vaccines have been proven to be safe and effective in several clinical trials and field settings [106].

### Treatment

Treatment with fluoroquinolones, azithromycin and third-generation cephalosporin drugs is the main treatment of choice [46], with chloramphenicol used in regions where there are susceptible strains. In 2003, the WHO recommended the treatment of uncomplicated typhoid fever to include ciprofloxacin, chloramphenicol, amoxicillin and co-trimoxazole [105].

### Conclusion

The current status of *Salmonella* infections in Africa calls for new strategies and resources in order to curb infections. The introduction of simple, more specific methods of diagnosis at an affordable cost will be of immense benefit to healthcare givers in tackling *Salmonella* infections in Africa. The prevention control strategy should include health education, sanitation improvements and good water quality. In the area of increasing antibiotic resistance to *Salmonella typhi*, vaccination should be considered for both vulnerable children and adults in order to prevent the disease, since the disease burden is high in Africa.

### Compliance with ethical standards

**Conflict of interest** The authors hereby declare that there is no conflict of interest.

**Ethical approval** This article does not contain any study that required ethical approval.

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