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*Review*

# Public health burden of non-typhoidal Salmonella strains in sub-Saharan Africa

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**The impact of non-typhoidal *Salmonella* (NTS) infections on human and animal health, with the associated morbidity and mortality is a global issue of public health concern. The socioeconomic conditions in the developing countries particularly the sub-Saharan Africa seem to further aggravate the rate and seriousness of the infections. Thus the endemicity of NTS infections to sub-Saharan Africa as well as the resistance of the NTS strains to both antimicrobials and environmental stress is shown in this review. The association of *Salmonella* virulence plasmids with both antibiotic and stress resistance genes could play a major role in the persistence and spread of the resistance and virulence genes in *Salmonella* and other related pathogens. This may constitute a serious public health challenge in resource-limited rural African settings**.

**Key words:** Non-typhoidal *Salmonella*, antimicrobials, stress, resistance, Sub-Saharan Africa.

## INTRODUCTION

Salmonellosis is a bacterial infection of both humans and animals caused by various strains of *Salmonella* species. Human typhoidal salmonellosis is caused by host-specific *S. typhi* and *S. paratyphi* with enteritis as the major clinical symptom. The World Health Organisation estimates global incidence of typhoid fever to be 22 million cases resulting in 200,000 deaths annually (Crump et al., 2004). Non-typhoidal salmonellosis on the other hand is caused by the generalist serotypes of *Salmonella* such as *S. typhimurium* and *S. enteritidis* which are collectively known as non-typhoidal *Salmonella* (NTS). These organisms cause disease in a wide range of hosts, usually with high morbidity and low mortality (Uzzau et al., 2000). They were recently reported to be responsible for about 3.4 million cases of invasive disease in humans annually (Ao et al., 2015). NTS infections cause clinical syndromes in humans which include diarrhoeal disease (gastroenteritis), invasive bacteremic illness and focal suppurative infections, aside asymptomatic carrier condition (Gordon, 2008). In immunocompetent individuals, the disease may be restricted to self-limiting diarrhea that does not require hospitalization. However, immunocompromised patients may present with primary bacteremia or other extraintestinal forms with high morbidity and mortality (Dhanoa and Fatt, 2009). The gastroenteritic disease is usually characterized by fever, abdominal cramps, nausea, vomiting and watery diarrhoea which can sometimes contain blood and mucus. Clinical manifestations of the disease can set in as early as 6 to 72 hours post exposure to *Salmonella*, and can last for 4 to 7 days (Zand et al., 2003). In Sub-Saharan Africa, the socio-economic burden of the disease is difficult to quantify due to lack of a standard method of assessment compounded by under-reporting in many cases. In addition, there is usually no reliable data in many of the countries from which informations can be obtained for proper analysis of the disease cost per case. In the U.S however, direct cost of human salmonellosis is usually measured in terms of medical costs and loss in productivity. The average economic burden of salmonellosis was estimated to be $210 per outpatient, $5,797 per inpatient with gastrointestinal infection, $16,441 per inpatient with invasive infection and $4.63

million per premature death (Adhikari et al., 2004).

## MATERIALS AND METHODS

The informations used for this review were obtained from published journal articles comprising of original research reports and meta-analysis studies. The materials, written in English language, were sourced from electronic databases, mainly Medline (Pubmed) and Oxford Academic

### Epidemiology of human non-typhoidal salmonellosis

*Salmonella* infections continue to have a serious impact on human and animal health globally, causing significant morbidity and mortality with serious socioeconomic effects (Cooke et al., 2007). The World Health Organisation (WHO) estimated an annual incidence of 1.3 billion cases of diarrhea due to NTS, resulting in about 3 million deaths (Maripandi and Salamah, 2010). The endemicity of NTS infections to the sub-Saharan Africa, where the invasive form has been rated as the commonest or second commonest cause of bacteremia in children and neonates has been established by several studies (Berkley et al., 2005; Graham, 2010). For instance, the incidence of 88 cases of NTS bacteremia per 100,000 persons/year was noted in children under the age of 5 years in Kenya (Morpeth et al., 2009). Similarly, an estimate of 7,500 NTS bacteremia cases per 100,000 persons/year was reported among adults with CD4 cell counts of less than 200 cells/$mm^3$ in Uganda (Sigauque et al., 2009). In Mozambique, children aged 15 years and below recorded childhood bacteremia cases as high as 120 per 100,000 persons/year (Feasey et al., 2010). Despite the fact that NTS cases are usually underreported, 1,318 cases of infective NTS were microbiologically confirmed in South Africa between years 2003 and 2004, with *S. typhimurium* and *S. enteritidis* as the most common serovars (Martinson et al., 2007). In addition, an autopsy study was carried out on 50 patients who died with a pre-mortem clinical diagnosis of tuberculosis. About 94% of the patients were HIV-positive and 23% of the HIV-positive patients were harbouring splenic NTS. Incidence of NTS bacteremia of 262 cases per 100,000 persons/year has been demonstrated in children less than 29 months old, in an evaluation of the impact of pneumococcal conjugate vaccine in Gambia (Enwere et al., 2006). Milledge et al. (2005) similarly described invasive NTS as the second commonest cause of invasive bacterial infectious disease in Malawian neonates, with about 62% mortality. Another study by Gordon et al. (2002) on NTS bacteremia among HIV-infected adults in Malawi showed that the disease has a high mortality of 47%, with 43% recurrence rates in the HIV-infected patients. In Ghana, although the studies of Labi et al. (2004) recorded low incidence of NTS bacteremia (6.5%), a prevalence of 57% in infant bacteremia has been documented (Evans et al., 2004). The prevalence of *S. typhimurium* ST313 causing gastrointestinal infections and septicaemia in patients in Nigeria and Democratic Republic of Congo was reported by Leekitcharoenphon et al. (2013). Other reports on *Salmonella* infections point to the fact that *S. typhimurium* ST313, which is also multidrug-resistant may be more associated with invasive salmonellosis (Feasey et al., 2012). Kingsley et al. (2009) suggested that the association of *S. typhimurium* ST313 with invasive infections might be due to its adaptation to the human host as a result of genome degradation either by formation of pseudogenes or chromosomal deletions. The study of Parsons et al. (2013) however revealed that *S. typhimurium* ST313 is not host-restricted as the pathogen is capable of causing infection in chicken, a non-human host. Invasive NTS infections are also sometimes accompanied by high case-fatality rates particularly in immunocompromised individuals. Gordon et al. (2002) and Brent et al. (2006) noted NTS infection case-fatality estimates of 4.4 – 27% for children and 22 – 47% for adults respectively among hospitalized patients in Africa. In another report, Gordon (2008) estimated case fatality from invasive salmonellosis in African adults and children to be 22 – 25%. Similarly, non-typhoidal *Salmonella* was isolated from up to 35% of HIV-infected African adults with documented bloodstream infections and mortality rate of 35 – 60% (Hohmann, 2001; Kankwatira et al., 2004). Keddy et al. (2009) reported *S. typhimurium* as a major opportunistic pathogen particularly in HIV-positive individuals.

### Risk factors of Salmonella infection

Although the risk factors for NTS infections in Africa have not been properly characterized, they may broadly be categorized into environmental and host factors. The environmental factors include food/water contamination, nosocomial infections, direct/indirect contact with animals, and transmission between humans (Morpeth et al., 2009). It is thought that poor socioeconomic conditions in rural African settings, coupled with lack of access to clean water and proper waste disposal may also be responsible for the high burden of the disease (Majowicz et al., 2010). Host factors however, include age, malnutrition, disease conditions (e. g. sickle cell, malaria, schistosomiasis and HIV infections) and recent antibiotic use (Berkley et al., 2005; Enwere et al., 2006). The relationship between malaria and NTS bacteremia has well been established in Africa, particularly in children (Takem et al., 2014). In Malawi, 4.6% of children with severe malaria had bacteremia, with NTS accounting for 58% of the cases (Bronzan et al., 2007). Park et al. (2016) in their multicenter study in 13 sites across sub-Saharan Africa, found a positive correlation between invasive NTS disease and malaria endemicity. Furthermore, a study carried out in mice co-infected with malaria and *Salmonella* revealed that the host defense against malaria infection is accompanied by high susceptibility to NTS bacteremia (MacLennan, 2012). NTS infections appear to be age specific with higher prevalence

in children less than 3 years old and adults above 50 years of age (Sigauque et al., 2009). In addition, recent antibiotic use coupled with malnutrition can destabilize normal intestinal flora and compromise mucosal integrity thereby increasing the risk of NTS gastroenteritis (Morpeth et al., 2009). Individuals with severe clinical immunosuppression are more prone to NTS infections and usually present with primary bacteraemia, leukopenia and opportunistic infections without gastroenteritis (Dhanoa and Fatt, 2009). For instance, HIV-infected persons have higher risk of NTS infections compared with the general population (Gordon et al., 2008). Among these individuals, non-typhoidal *Salmonella* sp is one of the most common causes of bacteraemia, often multi-drug resistant and associated with high mortality (24% - 80%) and recurrence rates (43%) (Gordon et al., 2002; Kingsley et al., 2009). Surveillance studies showed the association of NTS infections with yearly seasonality, with highest incidence recorded during the summer months (Cho et al., 2008).

**Routes of transmission of NTS**

*Salmonella* is ubiquitous in nature and can be found in soil and water environments. However, intestinal tracts of both domestic and wild animals remain the primary reservoirs of NTS (Hendriksen et al., 2011). During slaughter, *Salmonella* is passed from the intestinal tract of the host, through fecal contamination, to meat products. Similarly, some *Salmonella* serovars particularly *S. enteritidis* may colonise chicken ovaries and can be transmitted through eggs. Thus infection in humans may be acquired from contaminated meat or eggs, particularly when undercooked. Chicken meat in particular has been incriminated as the most probable route of NTS transmission (Morpeth et al., 2009; Hendriksen et al., 2011). It is however currently not clear if the product plays a role in the transmission of *S. typhimurium* ST313. Fruits and vegetables may also be contaminated with waste water from animal reservoirs, resulting in human infections (Hanning et al., 2009). Other additional routes of human infection by NTS have been postulated in developing countries and these include hospital acquired infection, direct and indirect animal contact with pet and food animals, and human–to-human transmission (Kariuki et al., 2006; Morpeth et al., 2009; Hale et al., 2012). The latter seems to be the common route in invasive NTS infections particularly in cases associated with *S. typhimurium* ST313.

**Pathogenesis of NTS infections**

Following ingestion of contaminated food/water, *Salmonella* in immunocompetent persons passes through the mucosa of the intestine and attaches to intestinal epithelia (Cooke et al., 2007). This is followed by invasion and intracellular replication of *Salmonella*, resulting in *Salmonella* containing vacuole (SCV). The SCV then contains large numbers of the bacteria within 6 hours post-infection. *Salmonella typhimurium*, as revealed by structural analysis, prefers to invade M-cells in the follicle-associated epithelium of Peyers patches and also the epithelial cells at the tips of absorptive villi (Santos et al., 2002). During invasion of epithelial cells, as demonstrated in bovine ligated ileal loop, *Salmonella* transits rapidly from apical location to basolateral location within 1 hour post-infection. This is followed by translocation into the lamina propria 1 – 2 hours after infection (Reis et al., 2003). The interaction of *Salmonella* pathogen-associated molecular patterns with Toll-like and NOD-like receptors leads to formation of inflammasome, together with activation and recruitment of neutrophils and macrophages as well as production of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α and IFN-γ) (de Jong et al., 2012). *Salmonella* during this process also translocates a number of effector proteins (SipA, SopA, SopB, SopD, SopE and $SopE_2$) into the host cell through Type III secretion system (TTSS-1). The TTSS-1 effectors trigger rearrangement of the cytoskeleton of the host cell and cause the formation of membrane ruffles coupled with bacterial internalization by macropinocytosis (Knodler et al., 2010). These trigger neutrophil influx leading to transepithelial migration of the neutrophils into the intestinal lumen (Zhang et al., 2003). The neutrophil influx in turn stimulates chloride secretion in intestinal epithelial cells followed by sodium and water to balance charge and osmolarity respectively. This leads to diarrhea accompanied by severe dehydration (Hopkins and Threlfall, 2004).

In HIV-infected persons, three mechanisms have been postulated as key contributors to the pathogenesis of invasive NTS. These include the loss of gut mucosal interleukin 17 cells which is thought to aid the dissemination of *Salmonella* organisms from the gastrointestinal tract to the bloodstream. Additionally, the accompanying loss in neutrophil chemoattraction results in absence of enteritis and further encourages *Salmonella* invasion (Gordon et al., 2002; Raffatellu et al., 2008). Secondly, there is humoral defect in which serum IgG antibodies directed against *Salmonella* inhibits the serum killing of NTS by other bacterial antibodies (MacLennan et al., 2010). Finally, a dysregulation in cellular cytokine production and attenuation of proinflammatory responses during intracellular infection encourages persistence as well as recurrence of invasive NTS (Feasey et al., 2012). Quantitative culture of blood and bone marrow by Gordon et al. (2010) during invasive NTS events in HIV-infected persons revealed that the organisms persist and replicate in blood and bone marrow.

**Virulence factors of Salmonella**

Virulence factors that are responsible for pathogenicity in enteric bacteria are often encoded by low-copy-number plasmids (van Asten and van Dijk., 2005). Virulence plasmids have only been found in *Salmonella* belonging to subspecies 1. In warm-blooded animals, the *Salmonella*

virulence plasmid is necessary for bacterial multiplication in the reticulo-endothelial system, thus indicating its importance in systemic infection (Baumler et al., 2000). The importance of the virulence plasmid in systemic diseases caused by NTS serovars is evidenced by the presence of the *spv* (7.8 kb region of *Salmonella* virulence plasmid) operons in strains that are more associated with disseminated infections e.g. *S. typhimurium* and *S. enteritidis.* The *spv* region of *Salmonella* subspecies I harbors five genes organized as a regulon viz; *spvRABCD*. Entry of *Salmonella* into macrophages/epithelial cells induces the expression of *rpoS,* which in turn regulates the expression of spvR. The latter (spvR) exerts the regulation of spvABCD (Marshall et al., 1999). Other virulence factors such as TTSS-1, Vi antigen, lipopolysaccharide (LPS) and other surface polysaccharides have also been characterised as major determinants of virulence in *Salmonella* (Thomsen et al., 2002; de Jong et al., 2012). However, the current virulence pattern of *S. typhimurium* ST313 and its restriction to the Sub-Saharan Africa has generated a lot of research interest in recent times. Boor (2006) associated the microevolution of the virulence gene expression in the organism with environmental stress. He concluded that perhaps the extreme draught followed by rainstorms, and hot days followed by cool nights in the Sub-Saharan African countries could have led to the emergence of the clone of *S. typhimurium*.

**Antibiotic resistance in NTS infections**

Non-invasive NTS infections may be self-limiting and may not require antibiotic treatment particularly in immunocompetent individuals. Contrariwise, invasive NTS infections manifesting as septicaemia, meningitis, etc, often require treatment with antibiotics, with or without hospitalizations. According to WHO guideline, the use of third-generation cephalosporins is advised for the treatment of invasive NTS, particularly where resistance to traditional first line antimicrobials such as ampicillin and chloramphenicol has been noted (WHO, 2009). As early as in the nineties, strains of NTS that were resistant to first line antibiotics have been reported, and recognised as an increasing problem in African countries such as Zimbabwe and Malawi (Rubino et al., 1998; Gordon et al., 2008). Third generation cephalosporins (ESCs) and fluoroquinolones therefore became drugs of choice for treating invasive NTS infections particularly in children (Threlfall, 2002). These treatment options were recently threatened by decreased susceptibility of the pathogens to the drugs as a result of *in vivo* acquisition of extended-spectrum β-lactamase (ESBL) or fluoroquinolone resistance genes, leading to treatment failure (Whichard et al., 2007). In the Democratic Republic of Congo, Lunguya et al. (2013) confirmed the presence of almost full multidrug-resistance among NTS strains isolated from human blood cultures. In Kenya, Kariuki *et al*. (2005) reported a rise in multidrug- resistant NTS from 31% in 1994 to 42% in 2005. In 1998 through to 1999 in South Africa, multi-drug resistant *Salmonella typhimurium* phage type DT104 strains were isolated from HIV-positive patients at the Chris Hani Baragwanath Hospital in Gauteng Province (Crewe-Brown et al., 2000). Feasay et al. (2014) similarly reported multidrug resistance in *Salmonella typhimurium* bloodstream infection in an HIV-infected patient in Malawi, who later died after two regimens of antibiotic treatment. In The Gambia and Senegal, Dione et al. (2011) found a significant association between virulence genes (*sopB*, *sitC*, *orfLC*, *pipD* and *pefA*) and resistance to commonly used antibiotics. Furthermore, the study of Leekitcharoenphon et al. (2013) showed that *S. typhimurium* ST313 isolated from Nigeria and DR Congo harboured resistant genes encoding $bla_{\text{TEM1b}}$, *cat*A1, *str*A/B, *sul*1 and *dfr*A1. Whole genome sequencing of a multiple drug resistant ST313 NTS isolate identified a distinct prophage repertoire and a composite genetic element encoding MDR genes located on a virulence-associated plasmid (Kingsley et al., 2009). The genetic basis for antibiotic resistance in NTS strains has been described in studies conducted in South Africa, Senegal and Mali. It was observed that most of the strains produced ESBLs such as TEM, CTX and SHV (Kruger et al., 2004; Harrois et al., 2013). This is a significant public health problem in Africa, with particular reference to treatment of serious non-typhoidal *Salmonella* infections in children in resource poor areas.

Although resistance to antibiotics can be natural, acquired resistance is of greater public health significance as it encourages the circulation of resistance genes within the environment. This threatens the effectiveness of prevention/treatment strategies of infections caused by bacteria and other classes of pathogens. Reduced treatment efficacy subsequently leads to increased cost of treatment, prolonged hospital stays and other complications as a result of failure to identify alternative antimicrobial. Acquired resistance in microbes is accomplished through acquisition of resistance genes by horizontal gene transfer (Carattoli, 2003). Resistance genes can either be located on extrachromosomal plasmids or on segments that originate from another genome and inserted within the chromosome. In the latter case, acquisition of the new gene may occur by genetic transformation or transduction. However, when resistance genes are located on plasmids, they can be mobilized by conjugative transfer at a very high frequency and efficiency and may involve simultaneous acquisition of several resistance genes (Waters, 1999). The exchange of the resistance genes can take place between non-pathogenic or environmental microbes and pathogenic organisms and this makes acquired antibiotic resistance a serious public health concern.

**Stress response in Salmonella**

*Salmonella* organisms encounter various environmental stresses within food, gastrointestinal tract and host immune system. Such stresses include temperature change,

nutrient deprivation, osmotic shock, pH extremes and DNA damage (Kenyon et al., 2002). Depending on the duration and severity of exposure, the stresses may inhibit the growth/survival and subsequently influence the virulence of the organism. Various genes can be induced under stress conditions, coding mainly for transcriptional stress regulator proteins. These proteins then activate other genes, including virulence genes, which are necessary for adaptation/survival of the organism in such stress conditions. Furthermore, response of bacteria to one stress can cross-protect the organism against other stress factors and cause changes in some aspects of the bacterial metabolism resulting in persistent, more resistant and dangerous pathogens (Shah, 2011). In addition, it has been shown that prior adaptation to mild or sub-lethal stress conditions triggers the release of shock proteins which enhance the survival of NTS strains in extremely harsh conditions (Ngwai et al., 2007). This has a significant implication on food processing particularly in rural Africa where heating at high temperatures are considered as primary methods of food treatment to prevent against food-borne illnesses.

## Conclusions

This review provides a picture of the endemicity of non-typhoidal *Salmonella* infections to the sub-Saharan Africa, and the antimicrobial resistance particularly of the invasive syndrome. The association of *Salmonella* virulence plasmids with both antibiotic and stress resistance genes as reported in some studies (Dione et al., 2011; Sirsat et al., 2011), could play a major role in the persistence and spread of both resistance and virulence genes in *Salmonella* and other related pathogens. This may constitute a serious public health challenge in resource poor rural African settings

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