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Comprehensive overview, molecular epidemiology and antimicrobial resistance in Non-typhoid *Salmonella*

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REVIEW

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ABSTRACT: Non-typhoid *Salmonella* poses a major threat to public health worldwide, impacting both human and animal populations across many countries. It is a leading bacterial pathogen causing diarrhea in humans, leading to gastrointestinal illness and, death. It is a significant contributor to food borne outbreaks and individual infections, particularly in low-income countries. Many virulence genes of *Salmonella* are clustered together on specific Deoxyribonucleic Acid segments known as *Salmonella* pathogenicity islands. Twenty-three *Salmonella* pathogenicity islands have been identified within the *Salmonella* genus, which are crucial for various virulence factors such as adhesion, invasion, intracellular survival, and replication. To prevent the spread of Non-typhoid *Salmonella*, it is crucial to enhance food safety practices and promote responsible antibiotic use. This review provides a comprehensive overview of Non-typhoid *Salmonella,* presenting information in a cohesive rather than fragmented manner. Unlike most research and reviews, which primarily focus on animal infections, this review specifically, concentrates on human Non-typhoid *Salmonella* infections.

KEYWORDS: Antimicrobial resistance, Antimicrobial resistance gene, *Salmonella*, Non-typhoid Salmonella, Salmonella pathogenicity islands.

INTRODUCTION

Salmonella infection, also known as salmonellosis, is the primary cause of food borne illness globally [1]. *Salmonella* is a rod-shaped, non-spore-forming bacterium that does not require oxygen to survive. It belongs to the Enterobacteriaceae family and is classified as Gram-negative [2]. *Salmonella* infections pose a significant public health threat, leading to substantial social and economic consequences [3]. Based on the clinical manifestations in humans, *Salmonella* infections are categorized into two types: non-typhoid *Salmonella* (NTS) and typhoid *Salmonella* [4]. While non-typhoid *Salmonella* serovars are commonly associated with diarrhea, they can also lead to systemic infections, known as invasive non-typhoid *Salmonella* (iNTS) disease [5]. NTS serotypes remain a significant cause of diarrhea [6]. Non-typhoid *Salmonella* serves as a prime example of the "One Health" concept, highlighting the interconnectedness of human, animal, and environmental health [7].

The serotype of *Salmonella* is determined by the organism's reaction to specific antibodies (antisera) against the somatic (O) and flagellar (H) antigens. This reaction, known as agglutination, classifies *Salmonella* into different serotypes [8]. The most prevalent NTS serotypes are *Salmonella typhimurium* and *Salmonella enteritidis*, which can infect a wide range of hosts [9]. *Salmonella typhimurium* has consistently been one of the most common serovars causing infections in both humans and animals globally [10]. *Salmonella enteritidis* and *Salmonella* typhimurium are responsible for over 40% of human salmonellosis cases globally and more than 70% of cases in Europe [11]. *Salmonella* is a leading cause of diarrheal disease globally, contributing to approximately 180 million illnesses and 298,000 deaths annually. This accounts for 9% of all diarrheal cases and 41% of deaths related to diarrheal diseases [2]. Non-typhoid *Salmonella* causes approximately 93 million intestinal infections and 155,000 related deaths each year [12].

Consuming contaminated food, especially those of animal origin like eggs, meat, poultry, and milk, is the primary way people contract *Salmonella* infections. Other foods, like fresh fruits and vegetables, have also been implicated in the transmission of *Salmonella* [14].

The world is currently facing an antimicrobial resistance (AMR) crisis, as bacteria are becoming increasingly resistant to various drugs used in both animal husbandry and clinical settings [15]. AMR can emerge through an evolutionary process where cells acquire random genetic mutations in existing genes and then transmit these mutations to their offspring through vertical gene transfer [16]. Antimicrobial resistance genes (ARGs) often exist in transmissible plasmids, which act as vectors for capturing and disseminating these genes among bacterial populations [17]. Many virulence genes contribute to the survival of *Salmonella* inside the host. Some of them are clustered in genomic regions known as *Salmonella* pathogenicity islands (SPIs) [18]. The most common antibiotic resistance profile found was resistance to ASSuT (ampicillin, streptomycin, sulfonamides, and tetracycline) [1]. Colistin, a critical antibiotic reserved for severe infections caused by bacteria resistant to multiple or most other antibiotics, is considered a last-resort treatment option [19]. *Salmonella* resistance to colistin is a more recent development compared to resistance to other antibiotics [20]. The common Extended-Spectrum β-lactamases (ESBL) encoding genes are CTX-M-1 group (82.7%) and TEM (17.3%). Additional genes are blaOXA gene, blaCTX of the CTX-M-9 group and blaSHV genes. CTX-M-1 and TEM confer resistance to extended-spectrum cephalosporins and penicillins, respectively. blaOXA, blaCTX-M-9, and blaSHV genes provide resistance to various beta-lactam antibiotics, including oxacillin and extended-spectrum cephalosporins [21].

The purpose of this review is to provide evidence on NTS, its molecular prevalence, antibiotic sensitivity profile, and antibiotic resistance genes on NTS. Specifically, it offers evidence regarding the risk factors associated with the infection, supports the development of an effective strategy for NTS control and prevention, strengthens and evaluates the efficacy of treatment strategies. It also helps to initiate integrated surveillance of *Salmonella* serovars in humans and animals.

RESULTS AND DISCUSSION

Classification of *Salmonella*

The genus *Salmonella* primarily consists of two species: *Salmonella bongori*, which is rarely linked to human infections, and *Salmonella enteric (*more commonly associated*). Salmonella enteric* is further divided into six subspecies [22]. The six subspecies of *S. enteric* are *enterica, salamae, arizonae, diarizonae, houtenae and indica* [23]. These subspecies have been further classified into over 50 serogroups and 2500 serovars based on their O and H antigens [24]. While over 2650 *Salmonella* serovars exist, a few have emerged as significant pathogens for both humans and animals [20]. The most common cause of gastroenteritis (NTS) are the broad host range serovars *S. typhimurium* and *S. enteritidis* [9]. The two serotypes are consistently ranked at the top (account for more than 40% of human salmonellosis worldwide and more than 70% of the human cases in Europe) [11]. Invasive non-typhoid *Salmonella* strains were responsible for approximately one-third of single-pathogen outbreaks between 2009 and 2015 [25].

Transmission, food sources and reservoirs

The primary sources of human *Salmonella* infection are food animals like cattle, poultry, and swine. Contamination of body of a dead animal that has been slaughtered for food with gastrointestinal content during slaughter is a major route of transmission [26].

While eggs and poultry meat are major sources of human *Salmonella* infection, recent outbreaks linked to pork consumption have highlighted pigs and pork products as a significant secondary source [27]. *Salmonella enteritidis* is primarily linked to poultry and poultry products, while *S. typhimurium* has a broader host range (affect both human and animal), including pigs, cattle, and poultry [24]. *Salmonella enteritidis*, a highly pathogenic bacterium, can infect a wide range of hosts and is commonly transmitted to humans through the consumption of undercooked or raw contaminated food, particularly meat and eggs [28]. Many animals, including chickens, pigeons, and reptiles, can serve as reservoirs for *Salmonella* bacteria. Humans are primarily infected through the food chain [3].

Clinical presentation and pathogenesis in immune competent hosts

Common initial symptoms of NTS infection include nausea, vomiting, and non-bloody diarrhea. Other possible symptoms are fever, chills, abdominal pain, muscle aches, joint pain, and headache. Less common symptoms include enlarged liver and spleen [29]. Infection with *Salmonella enteritidis* can cause fever, diarrhea, abdominal pain, and in severe cases, arthritis, meningitis, urinary tract infections, and even death [28].

Non-typhoid *Salmonella* infection is characterized by acute inflammation of the intestines, leading to inflammatory diarrhea. These symptoms are triggered by a rapid immune response to *Salmonella* surface

molecules like lipopolysaccharide (LPS) and flagellin, following bacterial invasion of the intestinal lining that enable it to adhere to cells, invade tissues, survive within host cells, and replicate [30].

Salmonella pathogenicity islands (SPIs)

Salmonella's pathogenicity is largely due to genetic elements called pathogenicity islands (SPIs). These islands contain genes for infection and are acquired through horizontal transfer (transfer of genetic material between unrelated organisms that is not offspring). Virulence plasmids also contribute to *Salmonella's* ability to cause illness. Researchers have identified 21 SPIs, with 5 being particularly common [24].

SPI-1 causes cell damage, inflammation, and infection. SPI-2 is essential for systemic infection. T3SS-1 and 2 (type 3 secretion system 1 and 2) are found in SPI-1 and SPI-2. SPI-3 helps *Salmonella* survive in harsh conditions. SPI-4 helps it stick to cells. SPI-5 contains a protein for the T3SS. SPI-7 is only found in S. typhi. SPI-8 and SPI-9 contain genes for toxins and secretion systems, while SPI-10 contains genes for surface structures [24]. SPIs contain T3SS systems that inject bacterial proteins (effectors) into host cells. These effectors help *Salmonella* invade, interfere with host functions, and survive inside cells [18].

Salmonella's virulence genes are often found on SPIs. There are 23 SPIs in *Salmonella*, wich are crucial for causing illness and infecting specific hosts. *Salmonella's* ability to cause disease relies on genes that enable it to adhere to cells, invade tissues, survive within host cells, and replicate. Many of these genes are located on specific genetic islands called SPIs [31].

Antibiotic resistance genes (ARGs)

Antibiotic resistance genes are often carried by transposons, integrons, and plasmids. These elements can move between bacteria, and transposases help facilitate this transfer. Different types of plasmids also play a role in gene transmission [25]. ESBLs make many antibiotics less effective. These enzymes break down penicillins and cephalosporins but not cephamycins or clavulanic acid. ESBL are the most ARGs, which includes TEM (Temoneira), CTX-M (Cefotaximase-Munich) and SHV (sulfhydryl variable). These genes are often found on plasmids and can spread easily between bacteria. These plasmids may also contain resistance genes for other antibiotics like sulfonamides, aminoglycosides, and fluoroquinolones [21].

Molecular epidemiology

The World Health Organization (WHO) estimates that salmonellosis causes approximately 3 million deaths globally each year. This food borne illness poses a significant health risk, particularly in developing countries, where it remains a leading cause of illness and death [4]. *Salmonella* infections are most prevalent in regions with inadequate hygiene practices for food preparation, handling, and waste disposal [32]. The WHO reported in 2015 that NTS was one of the four leading global causes of diarrheal diseases. It affected 550 million individuals annually, including 220 million children under the age of five. Based on this research, the global impact of *Salmonella* was estimated to be between 31 and 211 million illnesses and 36,341 to 89,045 deaths. The disease burden was estimated to be between 2.4 and 6.2 million Disability-Adjusted Life Years (DALYs) [24]. According to the European Food Safety Authority (EFSA), *Salmonella* infections caused by NTS are among the top seven diseases associated with outbreaks of enteritis in Europe. Additionally, they are the third leading cause of diarrheal deaths [25].

Table 1. Comparison of NTS infection, hospitalization and death of in the United State and China

Metric	Countries		References
	United state	China	
Annual infection	1.35 million	70-80% of bacterial food poisoning and 899 outbreaks (2003-2017)	[13]
Annual hospitalization	26,500	11,351	[13]
Annual death	420	-	[13]

As shown in table 1, the annual number of *Salmonella* infections and hospitalization in the United States is significantly higher than in China. The United States has 420 annual deaths attributed to NTS infections, while data on annual deaths in China is not available.

A study conducted in public hospitals in Hong Kong has highlighted the significant global health burden imposed by NTS. In 2016, an estimated 197.35 million individuals worldwide experienced diarrhea caused by NTS, resulting in 84,799 death [6]. In Sub-Saharan Africa, invasive non-typhoidal salmonellosis poses a serious threat to approximately 1.9 million immunocompromised individuals, often leading to life-threatening bloodstream infections

[4]. Studies conducted in Burkina Faso revealed a 17.9% prevalence of *Salmonella enterica* among 201 samples. These *Salmonella* isolates were identified as belonging to 16 distinct serotypes, with *Kentucky*, *Derby*, and *Tennessee* being the most common [33]. Research conducted in Ethiopia has indicated that *Salmonella* is a prevalent issue, with isolation rates ranging from 3.8% to 15% [34]. Approximately 3.1% of food handlers at the University of Gondar cafeteria in Ethiopia were found to be carriers of *Salmonella* [32]. In Ethiopia, non-typhoidal salmonellosis (13.71%) and typhoid fever (8.95%) were identified as the second and third most common diseases, respectively, following intestinal parasites [4].

Causative agent of NTS infection

Salmonella typhimurium and S. enteritidis

A study conducted in China revealed that *Salmonella typhimurium* was the most prevalent serotype, followed by *Enteritidis* and *Derby*. While other serotypes like *London, Rissen, Corvallis, Meleagridis, Kentucky*, and *Goldcoast* have also shown increasing prevalence, the recent detection of new serotypes such as *Telkebier, Uzaramo, Changwanni*, and *Weltevreden* has complicated surveillance efforts and heightened the risk of outbreaks [13]. A study conducted in Shaoxing City, China, identified 50 serovars and 16 serotypes of NTS. The most prevalent serotypes were *S. I 4, 12: i: - ST34* (25.29%), *S. Enteritidis ST11* (22.99%), and *S. Typhimurium ST19* (2%) [2]. A study examining 930 *Salmonella* genomes in Brazil identified 46 distinct serovars. *S. enteritidis* (34.7%) and *S. typhimurium* (20.4%) were the most prevalent [16].

Salmonella typhimurium alone

A study conducted at a hospital in Shanghai, China, revealed that *S. typhimurium* is a significant *Salmonella* serotype globally [1]. A study analyzing 35,382 serotyped *Salmonella* isolates in China between 1982 and 2019 identified *Typhimurium* as the most prevalent serovar in the country [13]. A study conducted in Thi-Qar Governorate, Iraq, revealed that *S. Typhimurium* has consistently been one of the most commonly isolated *Salmonella* serotypes in both animal and human infections worldwide. In this particular study, *S. typhimurium* was the most prevalent serotype identified in human infections, accounting for 39.7% of cases [17]. Another study conducted in Iraq indicated that *S. typhimurium* was the most prevalent serotype, comprising 54% of all isolated strains [35].

Salmonella enteritidis alone

A study conducted at a hospital in Shanxi, China, suggests that *S. enteritidis* infections result in approximately 93.8 million illnesses and 155,000 deaths globally each year. Of these cases, approximately 80.3 million are believed to be food borne [28]. Multiple studies conducted across European countries have indicated that *S. enteritidis* is the leading cause of *Salmonella* infections worldwide, accounting for 40% to 60% of human cases and numerous food borne disease outbreaks. This serotype is particularly prevalent in Africa, Europe, North America, and certain regions of Asia [36].

Invasive non-typhoid *Slmonella* (iNTS)

Children with a malaria positivity rate of 30% or higher were found to have a significantly higher acute infection rate for invasive non-typhoidal *Salmonella* (iNTS) compared to those with lower malaria positivity rates [5]. The estimated annual incidence of iNTS in Africa ranges from 175 to 388 cases per 100,000 children aged 3-5 years and 2,000 to 7,500 cases per 100,000 HIV-infected adults [30]. The most prevalent serotypes of iNTS in sub-Saharan Africa are *S. typhimurium* (40%), *S. enteritidis* (12%), and *S. dublin* (11%) [5].

Associated risk factors for NTS infection

According to northeastern Algeria study, children between the ages of 2 and 14 are most likely to get typhoid fever, iNTS disease, and malaria. Being malnourished or having HIV (Human Immunodeficiency Virus) increases their risk [5]. Individuals with weakened immune systems, particularly young children, are at the highest risk of severe complications from *Salmonella* infections [3].

An Iraqi study revealed that children residing in households with piped water had a 4.7 times greater risk of *Salmonella* infection compared to those using reverse osmosis-treated water. Children living in households with domestic animals were found to have a 10.5 times higher risk of *Salmonella* infection. Children of caregivers with primary education had a 3.9 times higher risk of *Salmonella* infection compared to those with tertiary education. Exclusively breastfed children had a 0.4 times lower risk of *Salmonella* infection compared to exclusively bottle-fed

children. Children whose caregivers always washed hands after cleaning them had a three times lower risk of *Salmonella* infection [35].

A study conducted in Hong Kong revealed that children who consumed food from wet markets, restaurants, or farms had a higher likelihood of *Salmonella* infection. Additionally, having a household member experiencing gastroenteritis symptoms was identified as a risk factor. Interestingly, playing at indoor children's playrooms was associated with a lower risk of *Salmonella* infection [37].

A study of 423 food handlers at the University of Gondar cafeteria in Ethiopia revealed that 3.1% were infected with *Salmonella*. All infected individuals were female, and the highest infection rate was observed among those aged 28-37. Food handlers with less than a year of experience were more likely to be infected with *Salmonella*. Poor hand hygiene practices, such as not washing hands after using the toilet, touching dirty materials, or before food preparation, were associated with increased infection rates [32].

Antimicrobial resistance (AMR)

The WHO has identified AMR as one of the top ten global public health threats. The overuse of antimicrobials in animal production systems has contributed to the increasing resistance among *Salmonella* bacteria. AMR poses a serious public health risk, leading to severe illnesses, prolonged hospital stays, long-lasting disabilities, increased healthcare costs, overburdened healthcare systems, higher costs for alternative treatments, treatment failures, and higher mortality rates [38]. Bacteria can develop resistance to antibiotics through an evolutionary process. This occurs when random genetic changes happen in existing genes, making the bacteria less susceptible to antibiotics. These changes can then be passed down to future generations of bacteria through a process called vertical gene transfer (transfer of genetic material from parent to offspring) [16]. *Salmonella* bacteria have evolved to become resistant to multiple antibiotics, including fluoroquinolones, third-generation cephalosporins, and even colistin [39].

Factors attributed for antimicrobial resistance

None typhoid *Salmonella* have been found in both humans and food animals. This is concerning as global antibiotic use in livestock is increasing and is expected to rise significantly by 2030. Many studies have reported the presence of multidrug-resistant *Salmonella* strains in various food animals and their products, including cattle, poultry, and pigs [26]. Antibiotic-resistant *Salmonella* bacteria, especially those that can quickly develop resistance through the spread of genetic material, pose a major threat to public health, particularly in the food production industry, including livestock and poultry farming [25].

Antimicrobial susceptibility

A Taiwanese study revealed high resistance rates for several older antibiotics in *Salmonella*, including ampicillin, streptomycin, sulfamethoxazole, tetracycline, and chloramphenicol. Moderate resistance was observed for cefoxitin, gentamicin, trimethoprim, and cotrimoxazole. Nalidixic acid and ciprofloxacin demonstrated significant resistance. However, resistance to newer antibiotics like azithromycin, certain cephalosporins, colistin, and ciprofloxacin was low. Carbapenem resistance was extremely rare [17].

A study conducted in Vietnam identified *Salmonella* as the most prevalent bacterial species across various environments. The bacteria showed high resistance to quinolones, third-generation cephalosporins, penicillins, and aminoglycosides. A review of 55 studies revealed widespread resistance to ciprofloxacin, ceftazidime, ampicillin, gentamicin, sulfamethoxazole-trimethoprim, and chloramphenicol in humans, animals, and the environment. *Salmonella*, in particular, exhibited the highest resistance to ampicillin and sulfamethoxazole-trimethoprim [38].

A meta-analysis study in Africa revealed that a significant number of *Salmonella* isolates (92.1%) were either partially or fully resistant to one or more antibiotics. This trend was particularly evident in human isolates, with 86.8% showing resistance. Among the tested antibiotics, the highest levels of resistance were observed for streptomycin, sulfisoxazole, nitrofurantoin, kanamycin, and tetracycline. Notably, full resistance was most common for streptomycin, followed by cephalothin, ampicillin, and sulfisoxazole [5].

A study conducted in Gondar, Ethiopia, revealed that a significant proportion (46.2%) of *Salmonella* isolates exhibited multidrug resistance. In fact, all isolates were resistant to at least one antibiotic. The study found high levels of resistance to specific antibiotics: 69.2% of isolates were resistant to amoxicillin, 54.8% were resistant to ampicillin and 46.2% were resistant to tetracycline. However, the isolates remained susceptible to gentamicin, ceftriaxone, and nalidixic acid. 46.2% of the isolates were resistant to nitrofurantoin [32]. As indicated in table 2, cefazolin exhibited very high resistance in Shaoxing City, China, highlighting widespread drug resistance across various regions. This suggests that drug resistance is serious public health issue, particularly in Asia, with concerning trends for the effectiveness of certain medications since drugs may soon become ineffective.

Table 2. Drugs and resistance level for NTS infection among countries

Country	Drugs	Resistance level in % respectively	Multidrug Resistance	Ref.
Shaoxing city	Cefazolin, streptomycin, ampicillin, ampicillin-sulbactam, doxycycline, tetracycline, and levofloxacin	86.21, 81.61, 77.01, 74.71, 72.41, 71.26 and 70.11	>83.91%	[2]
Hong Kong	Ampicillin, tetracycline, ciprofloxacin, chloramphenicol, and cotrimoxazole	76.0, 60.4, 56.0, 25.0 and 23.0%	-	[6]
Europe	Sulphonamides, ciprofloxacin, ampicillin and tetracycline	23.9, 27.3, 29.5 and 32.9%	-	[35]
America	Tetracycline, streptomycin, sulfisoxazole and ampicillin	55, 41, 38 and 38	-	[40]
Algeria	Ticarcillin, amoxicillin, cotrimoxazole, gentamicin, aztreonam, cefotaxime, ciprofloxacin, and amikacin	56.75, 45.94, 24.3, 24.3, 18.9, 16.2, 13.5 and 10.8	-	[33]

***Salmonella typhimurium* AMR alone**

A study conducted in Taiwan reveals that continuous exposure to antibiotics has resulted in the emergence of drug-resistant *S. typhimurium* ST313 [12]. Researchers discovered a highly drug-resistant strain of *S. typhimurium* that was impervious to 28 different antibiotics, including commonly used drugs like ceftriaxone, ciprofloxacin, and azithromycin [1]. An analysis of 556 *S. typhimurium* genomes identified 70 ARGs and 6 mutations linked to quinolone resistance. On average, each bacterial genome carried 7.8 genetic factors contributing to drug resistance [17]. Colistin is regarded as a "last resort" antimicrobial and is classified as "critically important" by the WHO. Unlike resistance to other antimicrobials, colistin resistance in salmonellae is a relatively recent development [20].

A study conducted in Taiwan has revealed a concerning increase in resistance to several antibiotics, including third-generation cephalosporins, cephamycins, ciprofloxacin, and azithromycin, among *S. Typhimurium* strains. Seven major clones of *S. Typhimurium* were identified, with four of them (HC100_2, 41, 305, and 310) exhibiting high levels of multiple drug resistance, affecting between 86.5% and 96.1% of isolates. Particularly worrisome are the pandemic multidrug-resistant clones HC100_305 and HC100_2, which account for a significant portion of the resistant strains [17].

A study conducted in Addis Ababa City, Ethiopia, revealed that all *S. Typhimurium* isolates were susceptible to ciprofloxacin and ceftriaxone. However, these isolates were resistant to ampicillin [4]. Reports indicate a rise in typhoid salmonellosis cases that are resistant to numerous drugs, including fluoroquinolones. Countries with a higher prevalence of multidrug-resistant typhoid *Salmonella* strains often report susceptibility rates to ciprofloxacin and other fluoroquinolones ranging from 44% to 59% [4].

***Salmonella enteritidis* AMR alone**

A study conducted in Tunisia evaluated the antibiotic susceptibility of *S. enteritidis* isolates using the disk diffusion method. Researchers tested 16 different antibiotics, including ampicillin, amikacin, chloramphenicol, azithromycin, ciprofloxacin, gentamicin, streptomycin, sulfamide, tetracycline, tigecycline, spectinomycin, kanamycin, netilmicin, nalidixic acid, pefloxacin, and trimethoprim. Out of the 45 isolates examined, 15 exhibited resistance to one or more antibiotics. Among these resistant isolates, four were exclusively resistant to nalidixic acid, ten were resistant to nalidixic acid and had intermediate resistance to pefloxacin, and one isolate was resistant to both nalidixic acid and ampicillin [31].

Antimicrobial resistance genes (ARGs)

Macrolides, tetracyclines, aminoglycosides, beta-lactams, and sulfonamides had the most resistance genes. Europe/North America had high macrolide resistance, while Asia/Africa had more sulfonamide/phenicol resistance. Tetracycline, aminoglycoside, and sulfonamide resistance was higher in Africa/Asia/South America [41].

***Salmonella typhimurium* ARGs alone**

Studies from Taiwan have shown that S. Typhimurium has become highly resistant to various antibiotics. This is largely due to the widespread dissemination of the DT104 clone, which carries a mobile genetic element known as SGI1. This element contains five resistance genes (bla CARB-2, floR, aadA2, sul1, and tet(G)) that confer resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines (ACSSuT). Furthermore, *S. Typhimurium* has also acquired resistance to fluoroquinolones, third-generation cephalosporins, carbapenems, azithromycin, and colistin [17].

Table 3. Most commonly identified antimicrobial resistance genes for NTS infections in different countries

Country	Antimicrobial resistance genes	Ref.
Taiwan	aadA2, aph(3")-Ib, aph (6)-Id, bla TEM-1 , floR, sul1, sul2 , and tet(A) , present in 34.7% to 52.9% of genomes.	[17]
Shaoxing city	aac(6')-Iaa (100%), blaTEM−1B (65.52%), and tet(A) (52.87%)	[2]
Hong kong	blaCTX-M-55, blaCTX-M-64, blaCTX-M-65 *S.* carbapenemase gene blaNDM-1, colistin resistance gene mcr-1, plasmid-mediated quinolone resistance (PMQR) genes [aac(69)-Ib-cr, qnrS1, and oqxAB]	[6]
Brazil	High rates of ARGs [tet(A), sul2, and fosA7] Intermediate rates of ARGs blaCMY−2, tet(B), aph(3")-Ib, aph(6)-Id, blaTEM−1B, and sul1.	[16]
Japan	Among the 9 clads, multiple resistance genes were detected in clades 1 &7. clades 1 aadA2, blaPSE-1, floR, and tet(G) & clade 7 isolates, including aadA1, aph(3=)-Ia, blaTEM-1B, sul1, tet(A)	[42]
America	Highest prevalence encoded by tetA (35%), tetC (20%), tetB (19%), and tetD (16%). For the aminoglycoside resistance included aadA5, aadA7, aadA12, aadA24, and aac(3)-Id, the most common aminoglycoside resistance genes were strA and strB for Sulfisoxazole resistance sul1 or sul2 (present in 39% and 66% . Among beta-lactam-resistant strains included blaCTX-M-14b, blaFOX-6, blaLAP-1, and blaOXA-2, Quinolone resistance is mediated by mutation of the quinolone resistance-determining regions (QRDRs) of gyrA, gyrB, parC, and parE	(18)
Yaoundé, Cameron,	All Salmonella isolates had the mdtk gene (fluoroquinolone resistance) and the sdiA gene (AcraB regulator). 52.63% had the macA gene (macrolide efflux and enterotoxin ST11 secretion). 47.36% had the marA gene (antibiotic and disinfectant export).	[15]

Note: aadA2=Aaminoglycosides resistance gene specially for gentamycine and streptomycine; aph(3") Ib and aph(6)-Id- Aminoglycosides resistance gene; blaTEM-1=Beta-lactams (specifically penicillins) resistance gene ; blaCARB-2 (blaPSE-1)=Beta-lactam antibiotics, specifically carbapenems resistance gene; blaCMY-2 and DHA-1= Beta-lactam antibiotics including, penicillins, cephalosporins, and cephamycins resistance gene; blaCTX-M-14, blaCTX-M-15 and blaCTX-M-65= Extended-spectrum cephalosporins (like cefotaxime and ceftriaxone) and often to penicillins resistance gene; Sull= Sulfonamides resistance gene; Flor= Fluoroquinolones resistance gene and tet(G) and tet(A)= tetracyclines resistance gene.

The table shows that *S. typhimurium* is increasingly resistant to multiple antibiotics worldwide. Asia, South America, North America, and Africa all have high rates of resistance genes, including those for aminoglycosides, beta-lactams, fluoroquinolones, sulfonamides, and tetracyclines. This growing resistance poses a major public health threat, requiring constant monitoring and effective control measures.

A newly identified gene, named dfrA34, was found to confer resistance to trimethoprim in *E. coli*, with a minimum inhibitory concentration (MIC) of 32 mg/L. This gene shares less than 50% similarity with other known dfrA genes at the amino acid sequence level [43].

An Italian study revealed a strong correlation between the presence of specific antibiotic resistance genes in *S. typhimurium* genomes and their observed antibiotic resistance phenotypes. The genes blaTEM-1B, sul1, sul2, tetA, and tetB were commonly identified. Additionally, point mutations in the gyrA and parC genes were detected, which are often associated with fluoroquinolone resistance. While various aminoglycoside-modifying genes were found, they did not appear to confer phenotypic resistance to aminoglycosides [11].

Three resistance genes were consistently found in all four highly resistant lineages in Ethiopia: the sulfonamide resistance genes sul1 and sul2, and the ESBL gene blaCTX-M-1. These genes contributed to multidrug resistance (MDR), pan-drug resistance (PDR), and extensive drug resistance (XDR) in these lineages [7].

***S. enteritidis* ARGs alone**

A study conducted at a hospital in Shanxi, China, revealed that 15 resistant *S. enteritidis* isolates carried mutations in the gyrA gene, which is associated with fluoroquinolone resistance. Additionally, one isolate was found to possess the blaTEM-1b gene, conferring resistance to ampicillin. No other resistance genes were detected in either resistant or susceptible isolates [31]. In addition to the rise in bacterial resistance to antibiotics, genes conferring resistance to specific drug classes have also emerged. These include genes associated with quinolone resistance (qnrA, qnrB) and β-lactam resistance (blaTEM, blaSHV, blaCTX-M, blaCMY-2) [28].

CONCLUSIONS AND FUTURE PERSPECTIVES

Salmonellosis continues to be among the major causes of illnesses and deaths around the globe particularly in developing countries. The widespread nature of salmonellosis and the spread of antibiotic resistance are of major concern for both developed and developing countries. Antimicrobial resistance in *Salmonella* varies not only by serotype, but also by source and geographical location. The most common salmonellosis are NTS of gastroenteritis and typhoid fever and the most common cause of NTS are the broad host range serovars *Salmonella enteritidis* and *Salmonella typhimurium* accounting for more than 40% of cases of salmonellosis in humans. The most frequently observed antibiotic resistance pattern was the ASSuT (ampicillin, streptomycin, sulfonamides, and tetracycline). The widespread use of antimicrobials at suboptimal doses and their prophylactic use in livestock, companion animals, and humans led to the emergence of drug-resistant *Salmonella* serovars to different groups of antimicrobial agents. The rise in antibiotics use led to the development of antibiotic-resistant *Salmonella*. Several factors have attributed to the rise in antimicrobial use especially in Africa and other low- and middle-income countries such as high burden of infectious diseases, poor antibiotic stewardship due to inadequate training of health professionals, lack of essential diagnostic equipment, widespread over-the counter (OTC) sale of antibiotics, and weak antibiotic regulatory environment. Addressing non-typhoid *Salmonella* involves a multifaceted approach that includes improved diagnostics, better food safety practices, research into antibiotic resistance, and global collaboration. By staying informed and proactive, we can better manage and reduce the impact of these infections.

DECLARATIONS

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Marew Alemnew designed and wrote the review; Aschalew Gelaw critically read and modified the review; Kindu Nibret and Addis Getu performed literature revision and took care of the editing of the review; Nega Berhane performed final revision.

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Data is available upon the request to the corresponding author.

Competing interests

The authors have no conflict of interest to disclose.

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