

Regional Review

An Algerian perspective on non-typhoidal *Salmonella* infection

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Abstract

Non-typhoidal *Salmonella* (NTS) represents a leading cause of food-borne disease worldwide. It is a global public health concern: more than 94 million cases and 115,000 deaths are reported every year, with a disproportionate impact in developing countries. The prevalence of multi-drug-resistant (MDR) *Salmonella* strains is another major health concern which affects antimicrobial treatment, as many studies report that infections caused by MDR strains are more severe than those caused by susceptible strains. In Algeria, NTS represent one of the primary causes of salmonellosis in both humans and food animal production, especially poultry. Epidemiological surveillance systems and monitoring programs for *Salmonella* infections are essential requirements to provide data useful for the effective detection and control of *Salmonella* outbreaks. The present review will supply a perspective on NTS infection, pathogenesis and antimicrobial resistance with a focus on the epidemiology of salmonellosis in Algeria.

Key words: Algeria; developing countries; multi-drug-resistant; non-typhoidal *Salmonella*

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Background

Salmonella infections are a primary concern for public health worldwide [1]. *Salmonella* is a Gram negative facultative anaerobe belonging to the *Enterobacteriaceae* [2]. *Salmonella enterica* is classified into more than 2500 serotypes based on two antigenic determinants: the somatic (O) antigen, and flagellar (H: phases 1 and 2) antigen [3,4] and clinically divided into two groups based upon the disease caused: typhoidal and non-typhoidal salmonellosis. Despite close genetic relatedness, typhoidal and non-typhoidal *Salmonella* (NTS) provoke different illnesses and a divergent response from the human immune system [5]. The Centers of Disease Control and Prevention (CDC) estimate that globally there are 94 million of cases of non-typhoidal salmonellosis, with 115,000 deaths every year [6]. Infection due to NTS is mainly associated with the consumption of contaminated raw meat, eggs and chicken, milk and other dairy products, fish and other sea foods, fruits and vegetables [7]. Food-borne NTS infection has a significant economic impact in both high- and low-income countries in terms of prevention and surveillance systems [8].

The concern with NTS infection has heightened after the emergence of multidrug-resistant *Salmonella* strains, as these pathogens are more virulent and responsible for adverse outcomes in infected patients [9]. In Algeria, several outbreaks of salmonellosis have been observed during recent years in both humans and food animal production, particularly poultry [10]. Lapses in hygiene practices are a major cause of food-borne NTS disease in humans, as well as the consumption of contaminated eggs and egg products with *Salmonella enterica* subspecies *enterica* serovar Typhimurium (hereafter *S.* Typhimurium) and *S.* Enteritidis [11].

Pathogenesis

NTS are transmitted by the oral–fecal route via contaminated food and water and are mostly associated with inadequate sanitation and hygiene [12].

NTS cause a gastrointestinal infection which presents as inflammation manifested with diarrhea, nausea, vomiting, and headache [13]. The severity of infection varies depending on two factors; the serotype implicated and the health of the patient [14]. Infants, the elderly, and immunocompromised patients are more

susceptible to NTS infections than healthy adults [14]. Although less common, some NTS actively invade intestinal epithelial cells using a type III secretion system (TTSS) to inject effector proteins into host cells, causing bacteremia [15].

Mechanisms of pathogenesis

A range of virulence genes contribute to *Salmonella* pathogenicity [16]. Virulence determinants can be harbored on the chromosome, usually encoded on pathogenicity islands, or on plasmids and bacteriophages [9]. Moreover, cells of *salmonella* are surrounded by an outer membrane containing lipopolysaccharide (LPS) which is able to release lipid A endotoxin, potentially causing shock in the host [17]. Another component of virulence is the ability to synthesize enterobactin [18]. Enterobactin is a siderophore secreted by *Salmonella* allowing it to sequester iron from the host and use it for growth [19]. *Salmonella* actively invade intestinal epithelial cells using a type III secretion system (TTSS) to inject effector proteins into host cells [15]. *Salmonella* pathogenicity island 1 (SPI-1) encodes genes required in the invasion process, while SPI-2 encodes genes involved in intracellular survival and replication in phagocytic and non-phagocytic cells, and has a crucial role in systemic infection [20].

Therapy for NTS infection

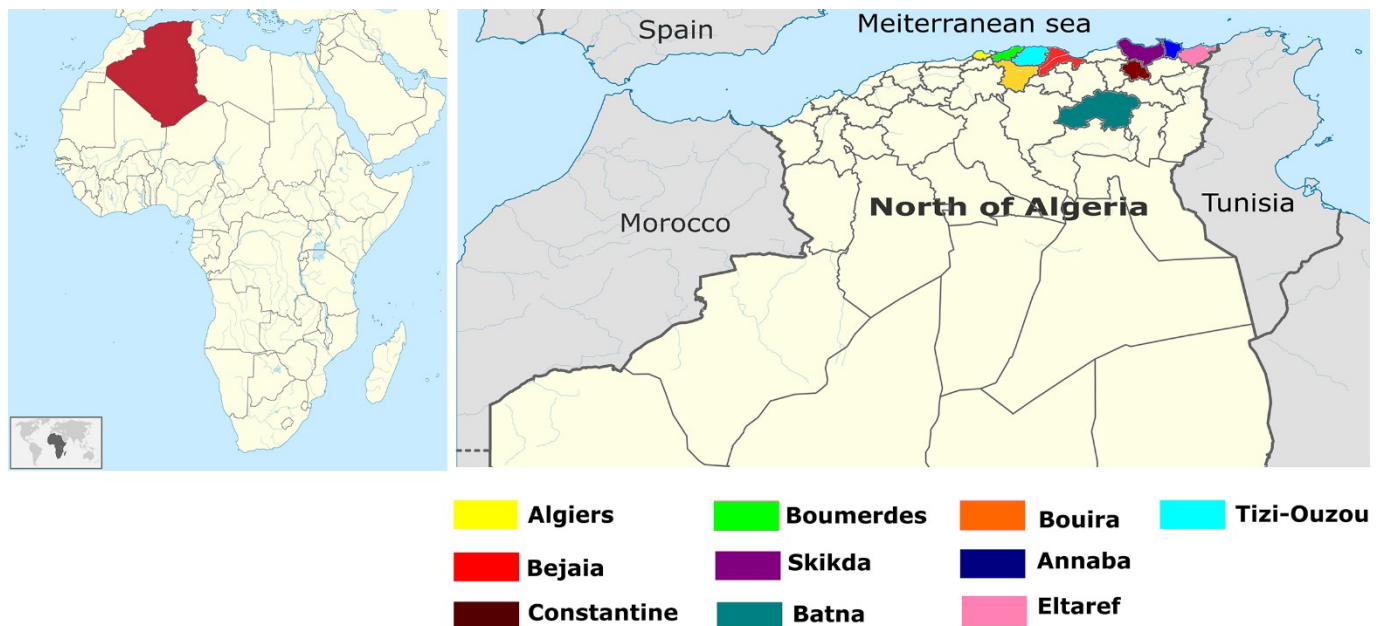
Treatment for NTS infection does not usually require antimicrobials, because these do not reduce the duration or acuteness of gastroenteritis, and instead may result in extended carriage and appearance of resistant strains [21,22]. Nevertheless, antimicrobial therapy is considered for patients with severe diarrhea [6], and is commonly used for invasive salmonellosis or when individuals with immunodeficiency are affected [22].

Salmonellosis in Algeria

Contaminated poultry meat is one of the main sources of food-borne *Salmonella* in humans [23]. According to the Global Food-borne Infections Network (GFN) there is a lack of surveillance projects and initiatives in many developing countries which has led to an underreporting of *Salmonella* serovars in humans and from food sources [24]. Poor diagnostic capacity contributes to a lack of available data in developing countries; in contrast most data on *Salmonella* serovar distribution are available from industrialized countries [25].

In Algeria, there are few studies on the spread and distribution of serovars, or antimicrobial resistance in NTS. One reported superficial *Salmonella* contamination in ovine and bovine carcasses sampled from the slaughterhouse [26] but the remainder which include *Salmonella* tend to focus only on isolates from

Figure 1. Geographical location and distribution of reported NTS infection with a focus on North Algeria. Colors represent cities where NTS infection has been reported in the last 12 years.



clinical or animal sources (essentially from broiler and/or laying-hen flocks) [10,27-29]. To date, these studies have been reported information from various cities in Algeria, including Algiers, Boumerdes, Tizi-Ouzou, Bouira, Bejaia, Constantine, Batna, Annaba and El Taref (Figure 1) and are summarized below [10,28-33].

One study from Algiers showed the detection of multiple *Salmonella* serovars contaminating a wide variety of raw meat and processed meat products, particularly from laying-hens [28,32] (Table 1). It is thought that this contamination probably takes place during meat processing at the retail level where more surfaces are exposed, as meat is deboned, cut into pieces, and minced [34]. Data from Batna, in eastern Algeria, identified the most common *Salmonella* serovars in broilers and laying breeding reproducers as *S. Typhimurium* and *S. Livingstone*, detected at a rate of 12% and 1.6 % respectively in poultry feces, cloacal swabs and dusty surfaces. In addition, all the *S. Typhimurium* isolates were resistant to ampicillin, ticarcillin, chloramphenicol and trimethoprim/sulfamethoxazole. These findings indicate that the local poultry industry is not compliant with Algerian biosafety legislation [10]. In Constantine (eastern Algeria), another study highlighted the huge prevalence of NTS in the broiler production chain in this region. It showed that 37% of broiler farms and

53% of slaughterhouses were positive for *Salmonella* upon inspection. Five serovars (*S. Hadar*, *S. Virchow*, *S. Infantis*, *S. Albany* and *S. Carnac*) were recovered from both types of site, with *S. Heidelberg* and *S. Rissen* only found on farms and *S. Typhimurium*, *S. Enteritidis* and *S. Montevideo* only found in slaughterhouses (Table 1). Among the 55 isolates of NTS, 51% (39/55) were MDR and 80% (44/55) showed resistance to at least one antibiotic including streptomycin, tetracycline, nalidixic acid and ofloxacin (Table 2) [29].

A preliminary investigation was conducted for the prevalence of *Salmonella* contamination in laying-hen flocks in the neighboring regions of Annaba and El Taref (Figure 1). The most prevalent serovars isolated were *S. Enteritidis*, *S. Kentucky*, *S. Hadar*, *S. Virchow*, *S. Heidelberg* and *S. Manhattan* (Table 1) [28].

During 2007, a surveillance study was conducted on different poultry farms in four Algerian cities: Tizi-Ouzou, Bouira, Bejaia, and Boumerdes which identified thirteen serotypes among 100 isolates (Figure 1, Table 1) [35].

In Skikda, persistence of gastroenteritis infection within the poultry industry prompted an investigation for NTS in this sector in 2013. Of 27 poultry houses, 34% were found to be contaminated with *Salmonella*; the main NTS serotypes isolated were *S. Kentucky* and *S. Heidelberg*, then *S. Enteritidis*, *S. Virginia* and *S. Newport* (Table 1) [33].

Table 1. Serotypes of Non-Typhoidal *Salmonella* isolated in different cities in Algeria.

<i>Salmonella</i> serotypes	City of isolation										Source of isolation	Study	Year of Isolation
	1	2	3	4	5	6	7	8	9	10			
<i>S. Anatum</i>	+			+							Red meat, human	[26, 27]	2006-08
<i>S. Altona</i>	+										Red meat	[27]	2007-08
<i>S. Corvallis</i>	+										Red meat	[27]	2007-08
<i>S. Enteritidis</i>	+	+	+	+	+	+	+	+		+	Red meat, poultry, human	[23, 24, 26-28, 30]	2005-09
<i>S. Typhimurium</i>	+		+	+		+				+	Red meat, poultry, human	[11, 26, 27, 30]	2006-08
<i>S. Livingstone</i>										+	Poultry	[11]	-
<i>S. Hadar</i>				+			+	+			Poultry	[23, 24]	2005-09
<i>S. Virchow</i>				+			+	+			Poultry, human	[23, 26]	2008-09
<i>S. Infantis</i>				+						+	Poultry, human	[23, 26, 28]	2008-13
<i>S. Albany</i>		+	+	+	+	+					Poultry	[11, 30]	2005-07
<i>S. Carnac</i>				+							Poultry	[11, 30]	2005-07
<i>S. Heidelberg</i>		+	+	+	+	+	+	+		+	Poultry, human	[24, 26, 28, 30]	2005-07
<i>S. Rissen</i>				+							Poultry	[24]	2005-07
<i>S. Montevideo</i>				+							Poultry	[24]	2005-07
<i>S. Blockley</i>				+							Poultry	[24]	2005-07
<i>S. Indiana</i>				+							Human	[26]	2006-07
<i>S. Kentucky</i>				+							Human	[26]	2006-07
<i>S. Senftenberg</i>				+			+	+		+	Poultry, human	[23, 26, 28]	2006-09
<i>S. Manhattan</i>							+	+			Poultry	[23]	2008-09
<i>S. Virginia</i>										+	Poultry	[28]	2011-13
<i>S. Newport</i>										+	Poultry	[28]	2011-13

1= Algiers. 2= Boumerdes. 3= Bouira. 4= Contantine. 5= Tizi-Ouzou. 6= Bejaia. 7= Annaba. 8=Eltaref. 9= Batna. 10= Skikda

These studies conducted on NTS infection in Algeria, provide evidence for the presence of highly drug resistant serotypes. The serotypes identified from broilers and human clinical cases in Algeria are largely similar to those usually present in broilers worldwide, particularly in Europe and the USA, as well as Africa [31,36,37]. This highlights that NTS infection and antimicrobial resistance are matters of concern in Algeria that need to be dealt with in a more comprehensive manner.

As in many other developing countries, Algeria is facing a paucity of data on NTS infection, probably linked to poor diagnostic capacity and lack of epidemiological investigation. Effort should be focused upon the design and implementation of strategies for laboratory-based surveillance, which will in turn

provide integrated data to public health authorities, allowing them to respond and intervene in NTS infection in an effective way.

Antimicrobial resistant *Salmonella* across Africa

Antimicrobials are used as common practice in modern food animal husbandry, for both therapeutic and prophylactic purposes [38]. Several studies suggest that antimicrobial resistance in NTS is promoted by the use of those antimicrobials in food animals [8,39-41]. The dissemination of Multi-Drug Resistant (MDR) *Salmonella* from animals to humans is a major adverse consequence for public health which is leading to a treatment failure in human infectious diseases [42]. Antibiotic resistance in NTS strains can be due to

Table 2. Antimicrobial resistance patterns of NTS in Algeria and some North African countries.

Country of isolation	Serotypes	Antibiotic resistance profile	Source of isolation	Study	Year of Isolation	
Algeria	S. Agona	AMP. CEF. CTX. SXT. SU. GEN. STR	Human	[26]	2006-07	
	S. Albany	NAL. OFX. STR	Human	[26]	2006-07	
	S. Enteritidis	AMP. CAZ. SU. TET	Human	[26]	2006-07	
	S. Hadar	AMP. NAL. OFX. STR. TET	Human	[26]	2006-07	
	S. Kentucky	AMP. CAZ, CEF. CTX. GEN. KAN. SU. SXT	Human	[26]	2006-07	
	S. Senftenberg	AMP. CAZ. CEF. CTX. GEM. KAN. NAL. STR. SU	Human	[26]	2006-07	
	S. Typhimurium	AMP. CHL. SU. STR. TET	Human	[26]	2006-07	
	S. Kentucky	AMP. CEF. STR. SXT. GEM. TET. NAL. OFX. ENR	Poultry	[23]	2006-07	
	S. Hadar	AMP. CEF. STR. TET. NAL	Poultry	[23]	2006-07	
	S. Albany	STR. NAL. OFX. ENR	Poultry	[24]	2006-07	
	S. Heilderberg	STR. NAL. OFX	Poultry	[24]	2006-07	
	S. Heilderberg	AMX. TIC. CTX. ATM. GEN. AK. SXT	Human	[28]	2001-13	
	S. Typhimurium	AMX. AMP. TIC. PIP. STR. NAL. SU. CHL. TET	Meat	[27]	2007-08	
	S. Anatum	STR. SU. TMP. SXT. F	Meat	[27]	2007-08	
	S. Altona	NA. Su	Meat	[27]	2007-08	
	S. Corvalis	SU	Meat	[27]	2007-08	
	S. Enteritidis	SU. F	Meat	[27]	2007-08	
	Tunisia	S. Enteritidis	AMP. NAL. CAZ	Human	[41]	2006-07
		S. Enteritidis	AMP	Human	[41]	2006-07
S. Enteritidis		N	Human	[41]	2006-07	
S. Enteritidis		AMP, TE	Human	[41]	2006-07	
S. Enteritidis		AMP, NA	Human	[41]	2006-07	
S. Typhimurium		AMP. NAL. GEM	Human	[41]	2006-07	
S. Zanzibar		AMP. TET. NAL. NEO. KAN	Human	[41]	2006-07	
S. Muenster		CHL. TET. NEO	Human	[41]	2006-07	
Egypt	S. Typhimurium	AMP. ERY. STR. TET. CO. SAM. SXT. CHL. NAL. GEM. AMC	Human	[13]	2014-15	
	S. Rubislaw	AMP. ERY. STR. TET. SAM. SXT. CHL. NAL. GEM. AMC	Poultry	[13]	2014-15	
	S. Kiel	AMP. ERY. TET. AMC	Poultry	[13]	2014-15	
	S. Derby	ERY. STR. TET. AMC	Duck	[13]	2014-15	
Morocco	S. Enteritidis	AMP. SXT. NAL	Human	[39]	2000-08	
Senegal	S. Kentucky	STR. KAN. TOB. GEN. AMK. SU. TMP. TET	Human	[40]	1999-09	
	S. Typhimurium	STR. KAN. TOB. GEM. AMK. SU. TM	Human	[40]	1999-09	

AK: Amikacin, **AMP:** Ampicillin, **AMX:** Amoxicillin, **ATM:** Aztreonam, **CAZ:** Cefazidime, **CEF:** Cephalothin, **CHL:** Chloramphenicol, **CO:** Ceftriaxone, **CTX:** Cefotaxime, **ENR:** Enrofloxacin, **ERY:** Erythromycin, **F:** Furan, **GEN:** Gentamicin, **KAN:** Kanamycin, **NAL:** Nalidixic Acid, **NEO:** Neomycin, **OFX:** Ofloxacin, **PIP:** Piperacillin, **SAM:** Ampicillin-Sulbactam, **STR:** Streptomycin, **SU:** Sulfonamides, **SXT:** Trimethoprim-Sulfamethoxazole, **TET:** Tetracyclin, **TIC:** Ticarcillin, **TOB:** Tobramycin, **TMP:** Trimethoprim.

genetic mutations or through the acquisition of resistance encoding genes on mobile elements [9]. Plasmids are typical carriers of determinants that confer resistance against conventional antibiotics such as ampicillin, chloramphenicol and tetracycline [43]. However, the chromosome can also harbor these determinants, *e.g.* on the multidrug resistance region of *Salmonella* Genomic Island 1 (SGI1) [9].

In Algeria, an increase in NTS has been observed among bacterial isolates in laboratories both clinically and in animals [30]. At present, the available data on NTS infection are not sufficient to understand the propagation of NTS through the food chain and into humans. One of the major consequences of such propagation could be resistance to antibiotics. More than 37% of broiler chain production were found to be infected with NTS in Constantine (Table 1) of which 51% were MDR [29]. A separate study showed 58% of 100 isolates demonstrated resistance to fluoroquinolones, particularly in *S. Heidelberg* [35]. It should be noted that an evaluation of risk factors showed that NTS infection in this region of Algeria is strongly linked to poor technical and hygiene practices [29].

The majority of antibiotic resistance determination in Algeria is based upon phenotypic characterization, and there is limited use of molecular biology to understand the spread of antibiotic resistance among food-borne bacteria. Multiple resistance types have been reported among different serotypes of NTS (Table 2), indicating the potential risk facing human health in the country through consuming food contaminated with resistant strains of NTS.

In Africa, the diversity of geography and low standards of living in many countries contribute to a lack of available data on NTS infection. Instead, estimations of the burden of drug resistant NTS infection must be made from isolated studies (Table 2).

In Morocco, during the period 2000 to 2008, outbreaks were reported with high levels of antibiotic resistant *S. Enteritidis* isolated from humans [44]. During the same period in Senegal, NTS serotypes isolated from patients showed an increase in resistance to amoxicillin from 0.9% to 11.1%, and nalidixic acid from 0.9% to 26.7%. Most of the NTS serotypes were *S. Enteritidis*, *S. Typhimurium* and *S. Kentucky* [45]. During 2006-2007 in Tunisia, several resistant NTS strains were isolated from human in different regions of the country, and most of them belonged to *S. Enteritidis* containing different patterns of resistance (Table 2) [46]. An Egyptian study conducted on *Salmonella* isolates from human and animals showed an increasing

rate of antimicrobial resistance among NTS isolates between 2014 and 2015, in particular to erythromycin and tetracycline, and amoxicillin-clavulanic acid. This resistance was linked to over-use of antimicrobials in livestock [13]. In Kenya, among 342 NTS isolates, the prevalence of MDR strains reached 42% during 2003 [47]. A more recent study in 2014 from Ghana reported high levels of MDR *Salmonella* phenotypes (n = 59/115, 51.3%) harboring resistance to ampicillin, cefuroxime, amoxicillin/clavulanic acid, chloramphenicol, cotrimoxazole and tetracycline [48].

In 2012, the European Food Safety Authority and European Centre for Disease Prevention and Control reported high levels of resistance to tetracyclines in NTS strains isolated in the EU, with a rate of 85% in poultry and 91% in swine. Similar rates of resistance were reported to sulfonamides and ampicillin. However, resistance to cephalosporins was low with maximum of 10% in both poultry and swine [37]. Reports from the National Antimicrobial Resistance Monitoring System (NARMS) in 2011 showed that NTS strains were isolated in the United States with high levels of resistance, particularly to penicillin, sulfonamides and tetracyclines in poultry, cattle and swine [49].

Epidemiology of NTS

As a result of consuming unsafe food, food-borne diseases have become a worldwide economic burden. Around 550 million individuals fall sick every year, including 220 million children under the age of 5 years [50]. *Salmonella* is one of the most reported causes of diarrheal disease globally [50]. In fact, the prevalence of *Salmonella* infection is higher than reported, because most infected people do not undergo copro-culture diagnosis [6].

Epidemiology related to NTS varies depending upon serovar, and its ability to cause gastrointestinal or invasive infection. With certain subtypes, *S. Typhimurium* is recognized as capable of causing bacteremia, whereas *S. Heidelberg*, *S. Dublin*, and *S. Choleraesuis* represent a significant potential to cause hospitalization, and even death. In comparison, serovar *S. Newport* was observed to cause fewer fatalities than *S. Typhimurium* [8].

Several outbreaks of food-borne infections of antibiotic resistant bacteria have been reported globally while individual epidemiology studies in more-developed African countries provide some basic insight until more data are available [51]. Such information is essential to understand the prevalence of multidrug-resistant *Salmonella* strains [45]. In Algeria, there are

very few epidemiological studies for NTS infection. During 2006 and 2007, a single epidemiological investigation was conducted on 100 strains of NTS from poultry and human clinical isolates in Constantine (Figure 1) in order to understand the contribution of avian NTS to human salmonellosis. Phenotypic and genotypic tests revealed a diversity among NTS serotypes (Table 2), but failed to confirm any association between the isolated serotypes even if they were collected in the same period of time [31].

In other parts of Africa, particular serovars are prevalent in specific regions, namely *S. Concord* in Ethiopia [52], *S. Bovismorbificans* in Malawi [53], *S. Stanleyville* and *S. Dublin* in Mali [54], and *S. Isangi* in South Africa [55]. In Kenya, an average of 166 per 100,000 children under five acquire an NTS infection every year [56,57]. In sub-Saharan Africa, a serious invasive form of NTS linked to *S. Typhimurium* sequence type 313 has emerged, and has become a leading public health issue in this region. This invasive *S. Typhimurium* had an estimated mortality rate of 20-25% in children and up to 50% in adults [58].

Food-borne *Salmonella* is the largest health burden of all bacterial pathogens in the US [59]. During 2014, a total of 19,057 laboratory-confirmed cases of food-borne infections were identified. *Salmonella* was linked to 7439 of these cases, in which 2144 persons were hospitalized, and among them 32 patients died [60]. The most commonly detected serovars of *Salmonella* in humans include *S. Enteritidis* and *S. Typhimurium*, followed by *S. Newport*, *S. Javiana*, and *Salmonella* with the antigenic formula 4, [5], 12:i:- [61].

Although developed countries have a better awareness among food handlers and optimized surveillance programs, NTS infection has been detected and considered responsible for patient morbidity and mortality for decades. For developing countries, the situation worsened by the limited sources currently available. Due to robust globalization and scanty *Salmonella* surveillance programs in most developing countries, the world is now dealing with a new challenge from *Salmonella enterica* spp. that are potentially multidrug resistant [38] and may spread all over the food chain [38,62]. In addition, massive human migration from African countries and an increase in food trade between developing and developed countries may play a role in spreading such isolates all over the world.

Conclusions

NTS infection is a global issue with a higher prevalence and burden in developing countries such as

Algeria. A strong foundation of reliable research data is needed to effectively describe NTS infection and trace public health consequences among the Algerian population. To achieve this aim, detailed national epidemiological and microbiological studies should be set up in order to evaluate the prevalence of NTS in every food of animal origin, determine which serovars are in circulation, and better understand the relationship between food production and outbreaks of human salmonellosis in Algeria.

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