Non-typhoidal Salmonella (NTS) infections: An overview

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Abstract

Non-typhoidal Salmonella (NTS) gastroenteritis is estimated to cause 93.8 million illnesses and 155,000 deaths each year across the globe. NTS has become one of the leading food-borne illnesses in immune-compromised people, elderly and children in both developed and developing countries including Kingdom of Saudi Arabia. NTS infection is caused by *Salmonella* species other than *Salmonella typhi* and *Salmonella paratyphi* A, B and C. Among more than 2,500 *Salmonella* serovars, Enteritidis is one of the most common serovars reported globally.

Wide range of hosts and drug resistance are the major reasons of increasing worldwide cases of NTS infection in human. The resistance rate varies with different serotypes and different antibiotics. *S. enterica* serotype Enteritidis, one of the most prevalent *Salmonella* serotypes, is relatively more susceptible to antimicrobial agents than are other serotypes. A much higher rate of resistance was found in *S. enterica typhimurium*, another globally prevalent serotype.

Occurrence of common strain types in NTS infections from across the globe and risk of increased morbidity and mortality in patients with resistant NTS strains require concerted efforts to combat the transmission of this ubiquitous infection.

Introduction

Non-typhoidal Salmonellae (NTS) are gram-negative, motile, and facultative anaerobic bacteria, which belong to genus Salmonella of Enterobacteriaceae family. The genus Salmonella consists of two species, i.e., *Salmonella enterica* and *Salmonella bongori* [1]. The most pathogenic species of Salmonella including NTS belong to the *Salmonella enterica* species [2, 3]. NTS have become the major cause of gastrointestinal infections across the globe. NTS usually causes self-limiting enteric diseases, however, NTS also cause severe invasive disease including bacteremia and meningitis among children, the elderly and immunocompromised patients [4]. Global estimates have revealed that 93 million enteric infections and more than 1.5 lac diarrheal deaths occur due to NTS bacteria every year [5]. Another study have shown that 1.2 deaths/100,000 population all over the world was due to NTS infections in the year 2010 [6].

The two prime contributing factors for increasing NTS infections is the ubiquitous nature of the pathogen and increasing drug resistance among NTS bacteria. Being ubiquitous, NTS can infect many host species to cause diseases [7, 8]. This host species ranges from companion animals to food animals and humans. Infected food animals play a pivotal role in enhanced transmission of NTS bacteria to human. Besides, increasing antimicrobial resistance in NTS has hampered effective treatment of infections [9-11]. Hence, patients suffering from the antimicrobial resistant NTS strains have shown to have increasing morbidity and mortality from across the globe [12-14]. Data from the Kingdom of Saudi Arabia (KSA) have also shown rising cases of NTS infections with both antimicrobial susceptible and resistant NTS strains from across the kingdom [2, 15, 16]. In the present paper we will review the global and local trend of NTS infections, and trend of antimicrobial resistance among NTS isolates.

Global view of NTS infections

 NTS is one of the major foodborne illnesses across the globe. It is cause of infection in human of all age groups including the very young and the old. NTS also infect groups of people with compromised immune system. NTS infections cause morbidity and mortality both in developing and developed countries with highest incidence in parts of Asia (3200 per 10000 person-years), Africa (320 per 100000 person-years), Europe (690 per 100000 person-years) and America (250 per 100000 person-years) [17]. Invasive NTS infection occurs when the organism spreads beyond the gastrointestinal mucosa to infect normally sterile sites such as the bloodstream, the meninges, bone, and joint spaces [18]. The studies based on US FoodNet data have reported that overall Salmonella infections leads to an annual incidence of 520/100,000 population, estimated 15 000 hospitalizations and 400 deaths per year [19]. The US FoodNet data has also reported 71% and 5.4% hospitalization and death among patients with invasive NTS disease, respectively. While in the patients with non-invasive disease these rates were substantially lower i.e. 17% and 0.2%, respectively. Data further report that the hospitalization and mortality rate significantly increase in patients older than 60 years [20]. Studies from England and Australia also report hospitalization of 1516 patients due to NTS infections resulting in death of about 1% of these patients [21, 22]. Additionally, analysis of a study from Denmark has also revealed the higher risk of mortality among the patients after salmonella infections than the control group over the period of time [24].

Occurrence of NTS in KSA

The cases of NTS infection vary from region to region in KSA. Table 1 summarizes the number of cases occurred in Saudi Arabia during 2011-2013. Makkah is the mass gathering place due to presence of pilgrims from across the globe. In the past decade, number of recorded cases of food poisoning by NTS has considerably increased during Hajj and Umrah seasons in Makkah [15]. This increased numbers of cases may have association with presence of large number of people from diverse socio-cultural background from across the globe. These pilgrims are forced to consume

food with compromised quality due to unavailability of affordable and hygienic food in the premises. Presence of food outlets with lower hygiene standards near by holy place are the highest risk factors to the people leading to foodborne diseases [23, 24].

Besides area of mass gathering, NTS infection cases have also been reported from other regions of KSA (Table 1). Such as, NTS food poisoning has also been reported from Riyadh [15]. Moreover, one-third of food poisoning outbreaks have been associated with NTS in Dammam, Eastern province of KSA [2]. In addition, a study has also shown that more than 40% of food infection cases were caused by NTS during 1999 to 2002 in Al-Hofuf [16]. Also, study from Najran has reported association of NTS bacteria as a major cause of gastroenteritis among children.

Predisposing factors for transmission of NTS infection

Ubiquitous nature of NTS bacteria, enabling it to establish infections in wide hosts range and

emergence of antimicrobial resistance among NTS are the two major contributing factors for the

increasing cases of NTS infections.

<u>NTS Transmission from wide host range to human</u>

Ability of NTS bacteria to cause infections in wide host range increases the risk of transmission of infections in human. Infected animals can present with a great variety of clinical symptoms, and risk factors for transmission to humans clearly differ by animal species, age groups, animal contaminated food with contamination originating from animal products, or contaminated food handlers, or contaminated processing equipment [25, 26].

Table 1: NTS infection in various regions of KSA during 2011-2013*

Regions	Infection/100,000 population		
	2011	**2012**	**2013**
Riyadh	473	367	285
Makkah	18	155	10
Jeddah	96	N/A	186
Taif	1	N/A	0
Madinah	14	16	51
Qasim	21	6	2
Eastern	580	525	546
Al-hasa	59	N/A	10
Hafr al-baten	10	N/A	0
Aseer	20	35	76
Bishah	30	N/A	6
Tabouk	0	0	2
Hail	0	0	1
Nortern	2	0	16
Jisan	3	2	1
Najran	47	23	11
Al-bahah	9	10	9
Al-jouf	0	2	0
Qurayyat	4	N/A	0
Qunfudah	7	N/A	1
Total	1394	1141	1186

* www.moh.gov.sa

Studies have shown that contact with animals remains a prime source of transmission of NTS

infection among human every year [27]. Cattle play a paramount role as source of foodborne

infection. Human *Salmonella enterica* serotype Newport outbreaks in Michigan in 2002 and 2004 were linked to cattle contact in a public setting [28-30]. Study from KSA has also shown presence of NTS bacteria in fifty percent of the meat samples collected from the butcher shops in Jeddah [31]. Moreover, nail biting, contact with manure, thumb sucking, eating, or having soiled hands and shoes have also been identified as a likely risk factors for animal-acquired NTS in human [32, 33].

Antimicrobial resistance among NTS

Increasing resistance in NTS species is becoming a grave concern, which result in difficulty in treating the infections [9-11]. Several worldwide studies have reported increasing morbidity and mortality in patients infected with antimicrobial resistant NTS strains [12-14]. The resistance rate varies with different serotypes and different antimicrobials. Although, occurrence of NTS infections and type of serovars reportedly vary with geographical location [34]. However, *Salmonella enteritidis* is the most common serovar reported from across the globe [35, 36]. Whereas the second most common serovar reportedly is *Salmonella typhimurium* [37, 38]. Despite of being the most common serotype, it is encouraging that the *Salmonella enteritidis* is relatively more susceptible to antimicrobial agents than the other serotypes. Such as, a much higher rate of resistance was found in *S. typhimurium*, as compared to other serotypes [39]. Moreover, *S. typhimurium* and other NTS species have exhibited resistance to multiple antibiotics including ampicillin, chloramphenicol, streptomycin, sulfonamide and tetracycline [40].

Another concern is the increasing resistance to nalidixic acid among several NTS serotypes, which also predicts increased resistance to fluoroquinolones (FQs), particularly ciprofloxacin [41-43]. The association of resistance to nalidixic acid with reduced susceptibility to fluoroquinolone has led to the treatment failure with ciprofloxacin among patients infected with NTS strains including *S. typhimurium* from around the world [11, 44]. NTS strains resistant to FQs are a serious problem in many areas. The prevalence or cases of NTS infections with FQs resistance have increased since 1997 reportedly [19, 45]. Africa, Europe, Vietnam, Pakistan and India have reported FQs resistance

rates ranging from 20% to 54% [34, 46]. Report from China has shown 8% ciprofloxacin-resistance among NTS. A study from Pakistan has also shown increasing resistance to FQs among NTS from 23% in 2002 to 50.5% in 2006 [46]. Moreover, resistance to FQs among NTS has also been reported from different regions of KSA as well. Such as reports from Dammam, Alhofuf and Najran have shown ciprofloxacin resistance among NTS isolates [2, 15, 16]. A recent study from KSA has shown about 65% and 36% of nalidixic acid and ciprofloxacin resistance among NTS isolates [47].

This trend is alarming since ciprofloxacin is currently the preferred treatment for severe Salmonella infections worldwide. Studies have shown that the patients infected with the nalidixic acid resistant *S. typhimurium* strains had 3-10 times higher risk of getting invasive infection and death [48].

Conclusion

Global occurrence of NTS infection with common strain types and similar trend of antimicrobial resistance despite of improved health care systems indicates successful adaptation of the NTS strains over the period of time. Higher occurrence of infection in the elderly people causes significant burden of hospitalization. Also, increased risk of morbidity and mortality in patients with antimicrobial resistant NTS strains require concerted efforts to improve diagnosis, patient management and prevention of this ubiquitous infection.

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