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Original Article

Typhoid and Non-Typhoid Salmonellosis Related Mortality in Iran, National Data from the Ministry of Health

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Abstract

Background: Despite the declining trend, salmonellosis is still an important preventable cause of death in Iran and the world, especially in certain age and occupational subgroups, and the need for preventive measures, especially raising awareness of at-risk groups, is necessary.

Methods: Data were obtained from the Ministry of Health covering the years 2013 to 2019. The data were then stratified by year, season, month, and province of death as well as sex, age group, belonging to rural vs. urban communities and cause of death and were then analyzed using SPSS to report differences in age, sex, seasonal patterns, and spatial distribution.

Results: Non-typhoid salmonellosis (NTS) and typhoid were recorded as the cause of 800 and 32 deaths, respectively, with the highest number in 2015 and 2013. Septicemia was the cause of 87.3% of deaths due to NTS, whereas typhoid was the cause of 62.5% of its respective cases. The highest percentage of death related to both occurred in spring (P<0.001). NTS mortality rates were higher in the 70-80 and 80-90 age groups, while typhoid mortality was greatest in the under 10 yr age group. NTS mortality was higher in urban while typhoid mortality was higher in rural areas (P<0.001). Most deaths occurred in Ardabil, Sistan and Baluchistan and Khorasan Razavi provinces and Sistan and Baluchistan, West Azerbaijan and Khorasan Razavi related to NTS and typhoid, respectively.

Conclusion: *Salmonella* remains a preventable cause of death, especially among the elderly and children, the data gathered in this study provides important information for priority setting in specific subpopulations and food safety policy.

Keywords: Iran; Mortality; Salmonellosis; Typhoid fever

Introduction

Salmonellosis, caused by both typhoid and nontyphoid *salmonella* strains, is one of the most prevalent foodborne diseases. Millions of cases and thousands of deaths are reported each year from all around the world (1).

Typhoid fever is a disease caused by *Salmonella enterica* serotype typhi (*S. typhi*). A mostly similar but

often less severe infection is caused by *S. paratyphi* A, B, and sometimes C (2). Like other typhoidal *Salmonella* serovars, *Salmonella Typhi* is restricted to humans as hosts (3). Generally, despite the great decline of typhoid due to access to safe and sanitary water in developed countries, it is still a serious public health issue in developing countries and both typhoid and paratyphoid fever are among the endemic diseases in Iran. The widespread prevalence of multidrug-resistant strains is also a significant concern (4).

Typhoid fever can spread through several pathways, including fecal-oral transmission and ingestion of contaminated water or food (5). Symptoms include prolonged fever, headache, nausea, loss of appetite, constipation, or diarrhea. The most common serious and lethal complication of typhoid fever is intestinal perforation. Although a great deal of improvement and progress have been made in patient care, morbidity and mortality rates are still high among patients suffering from typhoid perforation, mainly in low- and middle-income countries (6).

Nontyphoidal *Salmonella* (NTS) is one of the main causes of food-borne diseases, resulting in gastrointestinal infections that range from asymptomatic to severe clinical and systematic illnesses. Invasive NTS infections can be life-threatening, and they mostly affect infants and young children especially those struggling with malnutrition, the elderly and immunocompromised patients, including those infected with HIV and malaria. Known risk factors for NTS include consumption of contaminated food, like eggs, meat, vegetables, and dairy products (7, 8). The symptoms and severity of the disease depend on the characteristics of the serotype of the pathogen and the host. The symptoms usually include fever, abdominal pain, diarrhea, nausea and vomiting in some cases (9). The 2017 GBD study calculated that *salmonella enterocolitis* resulted in 95.1 million cases, 50771 deaths, and 3.10 million DALYs (10).

Previously in Iran, recording the data on food poisoning was not performed in most medical centers due to the short hospitalization time and outpatient treatment, for this reason, it was not clear which pathogen caused the poisoning. Fortunately, in recent years, the Ministry of Health and Medical Education has required hospitals and medical centers to diagnose and register the cause of food poisoning, in this regard, valuable raw data of this group of patients is available in various medical centers across the country. Analyzing these data in terms of recognizing risk factors related to a food poisoning can be effective in its preventing measures.

As little data exist on salmonellosis as a cause of death in Iran, the main purpose of this study is to use the national data on mortality related to both non-typhoid salmonellosis and typhoid and paratyphoid fever in the span of 2013-2019 to detect associated risk factors, with the aim for this knowledge to be used to reduce salmonellosis related death in the future.

Materials and Methods

Data on non-typhoid salmonellosis and typhoid and paratyphoid fever related death were obtained from the Ministry of Health, using ICD codes A01 for typhoid and paratyphoid fevers and A02 for other *salmonella* infections covering the years 2013 to 2019. The data were then stratified by year, season, month, and province of death as well as gender, age group, belonging to rural vs. urban communities and occupation. Raw collected data were coded and entered into SPSS, ver. 21.0 (IBM Corp., Armonk, NY, USA) data file. The data were then analyzed performing chi-square, binominal, and Kolmogorov-Smirnov tests to describe differences based on different demographic risk factors.

Results

Altogether 832 *Salmonella*-related deaths were identified during the span of the study from 2013 to 2019, 800 cases associated with NTS and 32 associated with typhoid fever. Most NTS related death happened in 2015 with 219 cases whereas most typhoid related death occurred in 2013 with 12 cases (Fig. 1).

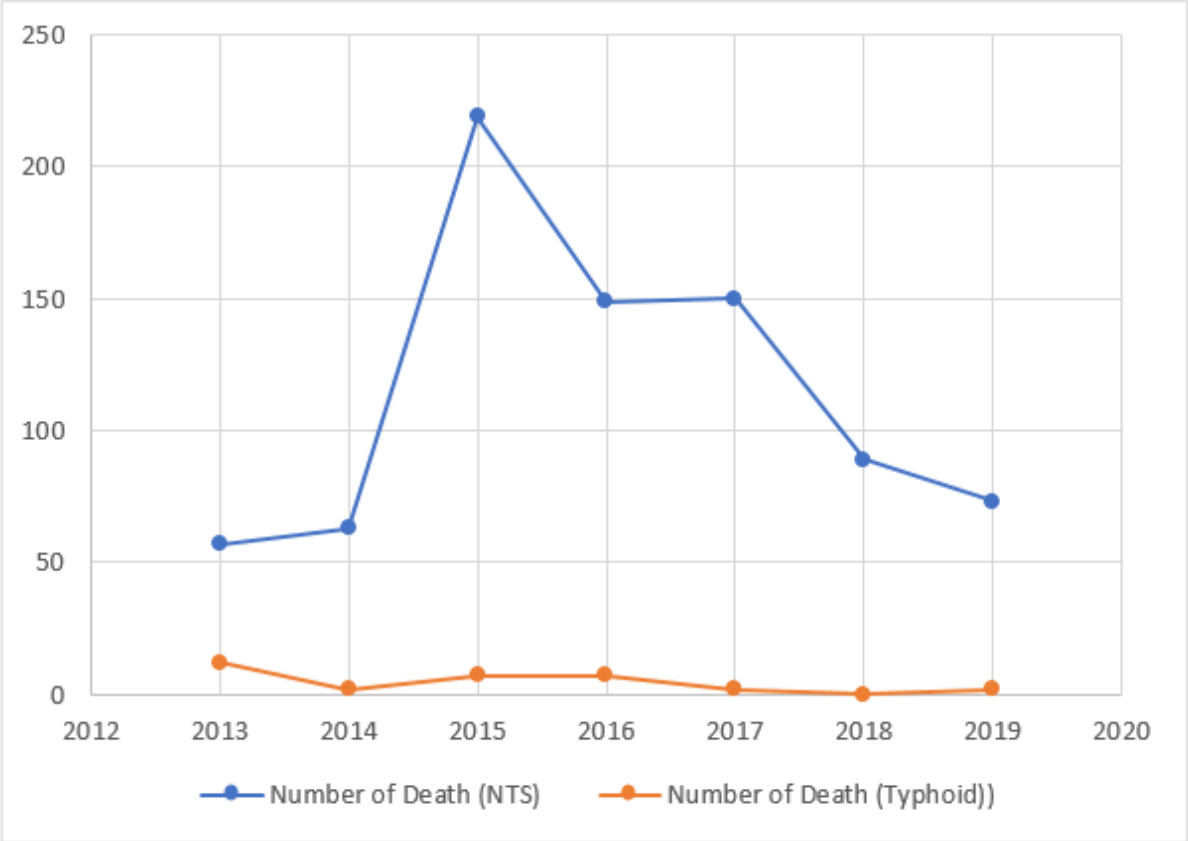

Fig. 1: Distribution of NTS and typhoid fever related mortality based on year of death during 2013-2019 in Iran Most NTS related death happened in 2015 with 219 cases whereas most typhoid related death occurred in 2013 with 12 cases.

Describing the seasonal pattern of salmonellosis related deaths in Iran, the most NTS-related mortalities occurred in spring with 29.1% of all deaths (P<0.001). Similarly, the most typhoid fever-associated mortalities happened in spring (37.5% of all deaths, P=0.355).

NTS related mortality was most prevalent in April and May, each with 84 cases and least prevalent in October with 48 cases (P<0.001). Most typhoid related death occurred in June with 8 cases while several months had only 1 case, however the results were not significant (P=0.141).

Mortality rates associated with typhoid fever were higher amongst the under 10 age group with 12 cases (37.5%, P<0.001). Interestingly, the age group of 20 to 30 had no deaths due to typhoid fever. The age groups of 70 to 80 and 80 to 90 account for almost half (46.2%) of the mortalities associated with NTS followed by the less than 10 age group 14.6% of deaths, while the age group of 10 to 20 shows the lowest occurrence with only 2.4% of cases. (P<0.001) (Fig. 2).

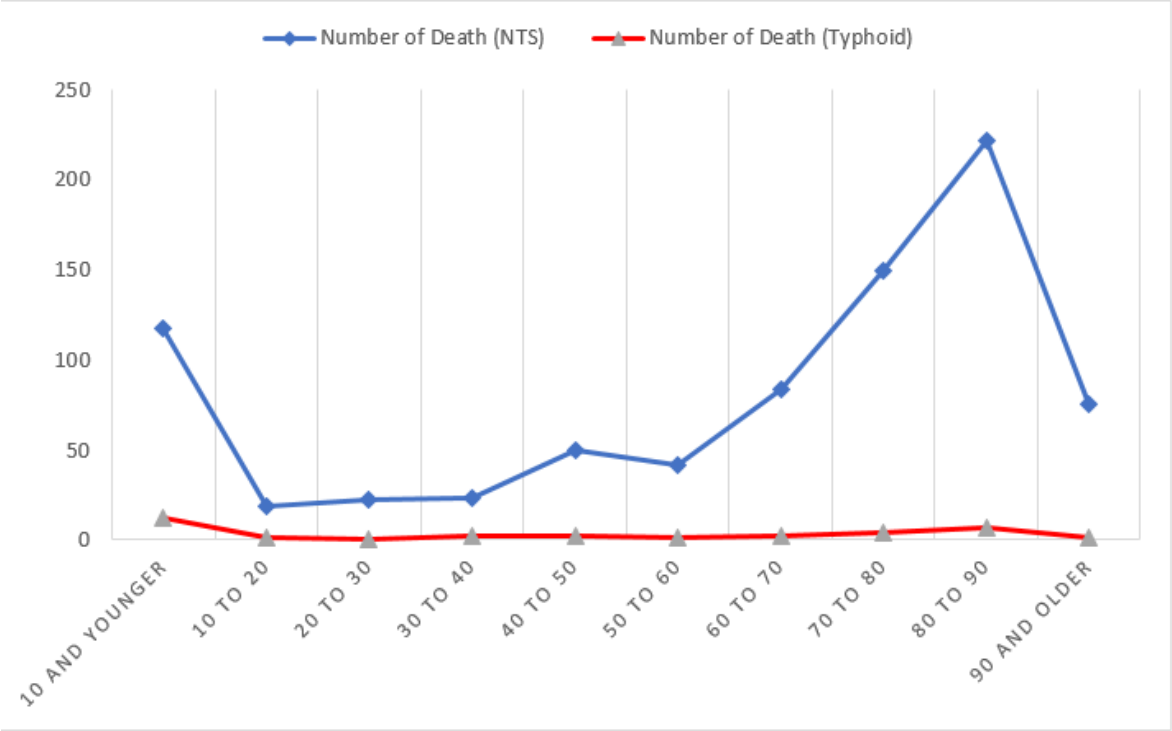

Fig. 2: Distribution of NTS and typhoid fever related mortality based on Age Groups during 2013-2019 in Iran. The age groups of 70 to 80 and 80 to 90 account for almost half of the mortality associated with NTS, while the age group of 10 to 20 shows the lowest. Mortality rates associated with typhoid fever were higher amongst the under 10 age group while no deaths was registered in the 20-30 age group

Although NTS related mortality was more prevalent in men (426 deaths, 53.3%) and typhoid fever related mortality in women (18 deaths, 56.3%). The results were not statistically significant according to the binominal test with p values 0.071 and 0.596 respectively.

NTS related mortality was higher in urban areas with 574 out of 800 cases. (71.8%, P=0.001) whereas typhoid related mortality was higher in rural areas with 20 out of 32 cases (62.5%, P<0.001). Assessing the frequency of deaths among occupational job groups revealed that housekeepers had the highest risk of mortalities related to both typhoid fever and NTS in Iran, 9.4% and 8.4% respectively. However, none of these findings were not statistically significant (P>0.05)

Assessing the spatial distribution of the disease in Iran, the most cases of typhoid related deaths occurred in Sistan and Baluchistan Province with 15 deaths of all (40.6%), while in many provinces no case was recorded (P=0.001). While most deaths associated with NTS occurred in the provinces of Ardabil (200 deaths, 25%), followed by Sistan and Baluchistan (132 deaths, 16.5%), and Khorasan Razavi (106 deaths, 13.3%) (Fig. 3), most deaths related to typhoid fever were occurred in Sistan and Baluchistan (Fig. 4).

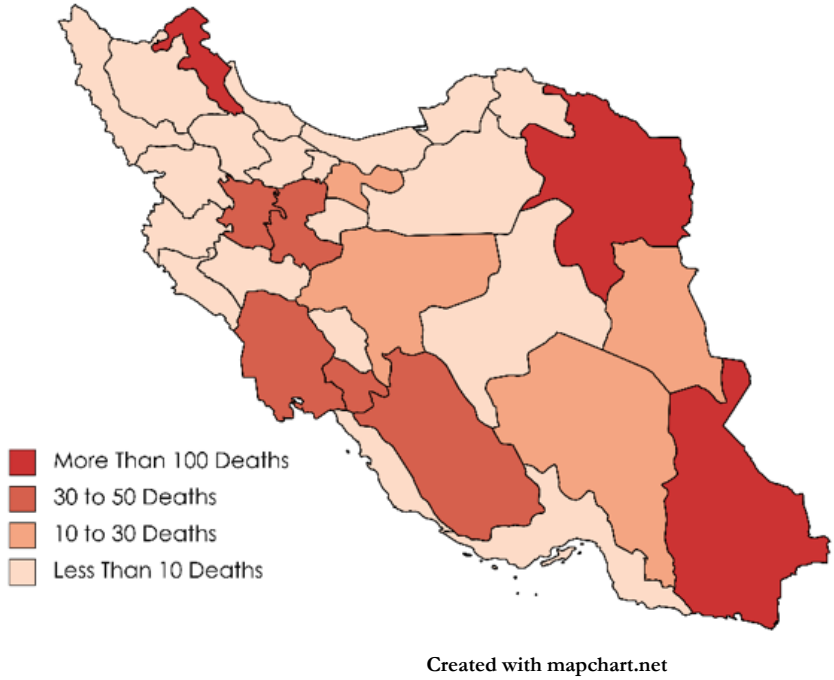

Fig. 3: Distribution of NTS related mortality based on province during 2013-2019 in Iran. Most deaths associated with NTS occurred in the provinces of Ardabil, Sistan and Baluchestan and Khorasan Razavi

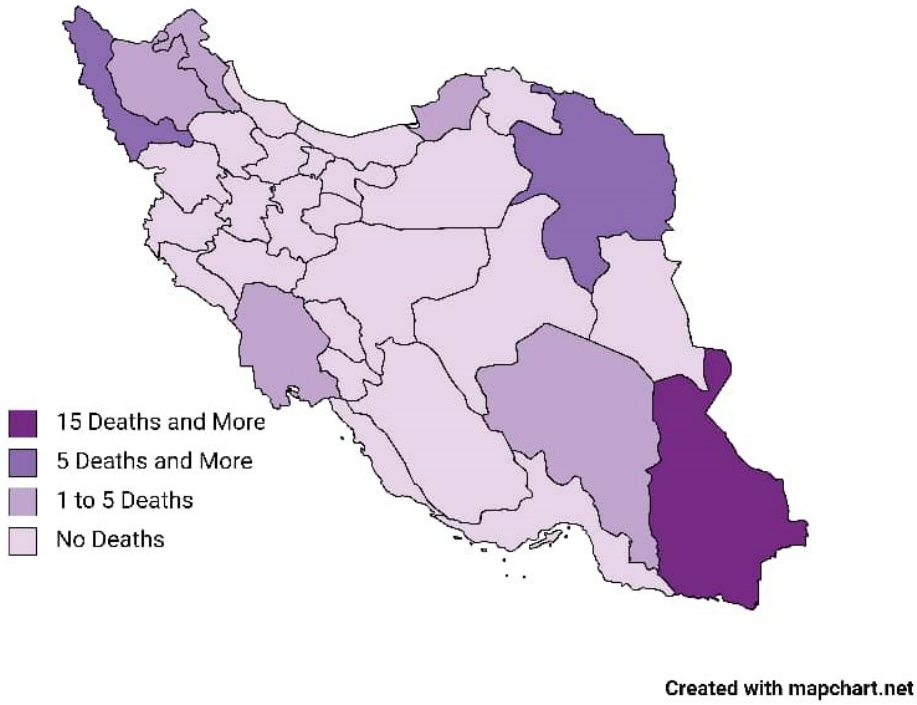

Fig. 4: Distribution of typhoid related mortality based on province during 2013-2019 in Iran. Most cases of typhoid related deaths occurred in Sistan and Baluchestan province with 15 deaths of all (40.6%), while in many provinces no case was recorded

Discussion

Enteric fever caused by *Salmonella enterica* serovars is a systemic infection manifest by prolonged high fever, malaise and headache that with no suitable treatment leads to gastrointestinal bleeding, septic shock, and death, whereas NTS species classically lead to diarrhoeal disease and rarely cause septicemia (11). On the other hand, NTS typically are a crucial cause of self-limited diarrheal illness transmitted via contaminated food or water (12). However, in a number of cases NTS involve blood circulation system and cause life-threatening infections and are the leading causes of death amongst food-borne bacterial gastrointestinal pathogens (13,14).

In a 6-year period of this study during 2013-2019, 32 typhoid related deaths were reported in Iran. The highest number of typhoid related death occurred at the beginning of the study in 2013 with 12 cases and falling trend in mortality was observed over the study period. Our results are parallel to global reports on typhoid and paratyphoid infections. Typhoid salmonellosis is relatively high in countries with poor water sanitation in south and southeast Asia, and sub-Saharan region in Africa particularly in children (15, 16). According to the systematic study of global burden of typhoid and paratyphoid fevers that published in 2019, 14.3 million cases occurred worldwide in 2017 showing 44.6% reduction compared to 25.9 million cases in 1990. Also, incidence rate of typhoid and paratyphoid salmonellosis is estimated 15 to >50 per 100,000 with mortality rate of 1-5 per million, in 2017 (17). Similarly, results of study in Pakistan-Iran's southeast neighbour- showed that 20 deaths from 2016 to 2018 were occurred due typhoid fever (6).

Based on the results gathered in a study that assessed the burden of the disease in low- and middle-income countries according to the World Bank classification, it is estimated that 1.6 billion people were at high-risk of typhoid fever worldwide and Iran with more than 100 cases per 100,000 people was classed as a high-risk area in 2014 (16). Although according to our study, the mortality rate has been declining from 2013 to 2019, but we still need a nationwide surveillance and control system for typhoid fever such as safe and sanitized water supply, timely diagnosis, and treatment of patients. Furthermore, for typhoid control in high-risk populations, WHO has suggested use of polysaccharide vaccine (17).

A systematic review that assessed the seasonal dynamics of typhoid and paratyphoid fevers, found the peak seasons for occurrence of typhoid fever to be from July to Nov in Africa and the Middle East (18). In accordance, our study also found that most typhoid related deaths happened in summer followed by autumn.

Universal age-specific incidence rates (ASRs) per 100,000 of typhoid and paratyphoid fevers are higher among children, especially 5 to 9 yr old children that show gradually declining into later life. In accordance our findings show a significant increasing mortality rate among children under 10 years old during 2013 to 2019 in Iran. Similarly, more than half of the hospitalized cases in Pakistan were between 2-10 yr old (6). Another study that had explored the pattern of morbidity and mortality of typhoid fever found that the highest typhoid associated mortality happens in children. Moreover, they showed that typhoid related death was more prevalent in women but similar to our study the results were not statistically significant (19).

In this study, most deaths related to typhoid happen in rural areas, low access to clean water and low hygiene education can be reasons for this finding. Besides, the most deaths of typhoid and paratyphoid fevers were occurred in Sistan and Baluchistan Province representing lack of access to safe water in rural and marginal areas of the province and Lack of health facilities in this deprived province in southeastern Iran which requires a lot of attention from government and health officials. According to our results, NTS related mortalities compromised 96.15% of all *salmonella*-related

deaths which shows a declining trend during the study period from 2013 to 2019.

According to WHO, in assessing the burden of 22 foodborne infections, diarrheal and invasive infection caused by Non-typhoid *Salmonella* had the highest burden (20).

Although NTS infections are on the decline, but they are still the reason for several recent multi-country outbreaks (21).

The global burden of NTS was high in 2010, with an estimated 93.8 million cases, of which 80.3 million were foodborne, and 155,000 deaths occurred in each year (22). On the other hand, 23,000 hospitalizations and 450 NTS related deaths occur annually in the United States (23). Moreover, Katiyo et al. in 2019 study about Epidemiology and Outcomes of NTS in England from 2004 to 2015, reported 155 cases of mortality out of which 120 (77%) patients age were over 65 yr old similar to our study where most cases were more than 70 yr old. Male patients with NTS were more likely than females to have bacteremia (24). Moreover, Cummings et al. found the mortality rates were higher in males in United states (1).

A study by Stephen and Barnett conducted in 2016 in Australia showed that 5 °C increasing in average temperature as well as 10 mm in rainfall were linked to amplifying in salmonellosis cases by 45% and 24%, respectively (1). Similarly, in this study, we showed that spring had the highest occurrence of NTS related deaths.

The high prevalence of mortality associated with NTS in urban areas of Iran may be related to consuming more unhealthy food in restaurants in those areas. The high rates of NTS related mortality in the provinces of Ardabil, Sistan and Baluchistan and Khorasan Razavi can be due to eating habits of the people like consumption of raw egg yolk. Additionally, low economic situation may result in people not seeking proper treatment.

Increasing occurrence of antimicrobial resistance in both typhoid fever and NTS is a serious public health problem as they are linked to poorer clinical outcomes and higher case fatality rates (10,25,26). This condition makes the governments and health administers to reinforce the preventive and controlling programs.

Conclusion

Salmonella remains a preventable cause of death, especially among subpopulations such as the elderly and children. These findings emphasize the significance of early diagnosis, well timed treatment, and the necessity for public health interventions to prevent foodborne infections.

Certainly, using the national data from registry of Iran ministry of health brings forth important information for priority setting in specific subpopulations and food safety policy. In light of our findings, there is still a continuous need to find and implement effective preventive measure programs in case of both typhoid fever and NTS all around the country focused on at-risk populations and high mortality areas such as Sistan and Baluchistan.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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