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Typhoid Fever Risk Factors and Challenges to Control: Narrative Review of the Scientific Literatures

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ABSTRACT

Typhoid has remained endemic in parts of Asia and Africa, where the morbidity and mortality are high. It is believed that among the factors responsible, lack of knowledge on risk factors and control challenges are important. Hence, the objective of this article was to generate a non-systematic narrative review on typhoid risk factors and control challenges which can be understood by majority of the stakeholders. Data sources used included reviews and original articles available from 1997 to 2019, from PubMed, Google Scholar, JSTOR, and Sciencedirect. 76 publications were included, and 20 risk factors and 6 control challenges were outlined. Some of the risk factors included contaminated water, contaminated food, contact with a typhoid carrier, contact with a typhoid patient, lack of proper handwashing, lack of vaccination, hot weather*,* and mechanical vectors, while some of the control challenges included increase in drug resistance, data unavailability, and vaccine limitations. Findings indicated that though typhoid is transmitted through the faeco-oral route, a number of risk factors play important roles in its transmission, and these factors are common in many regions of the world especially in developing and underdeveloped countries. Also, understanding the control challenges will guide provision of more efficient health interventions.

Keywords: Typhoid, Risk, Factors, Narrative, Review

INTRODUCTION

Typhoid fever results from infection with the bacterium *Salmonella typhi,* the resulting illness which affects many body organs has been a significant basis for many deaths, hospitalizations, and ailments, especially in developing and underdeveloped nations of the world where there are no proper hygiene systems and members of the populations in such areas usually utilize polluted sources of water and consume food materials invisibly soiled with fecal matter, which are the primary ways by which the pathogen is spread (Marchello et al., 2019).

This disease is believed to have resulted in 21·6 million infections and 216,500 mortalities worldwide in the year 2000 (Bhan et al., 2002), and amid 9.9 to 24.2 million illnesses and 75,000 to 208,000 mortalities per year by 2017, although information regarding the incidence of typhoid disease has been rare in small and middle-income states (Antillón et al., 2017).

The frequency of antibiotic-resistant *Salmonella typhi* infections has also been rising worldwide, thereby heightening the need for moving forward with an all-inclusive and wide-ranging plan for efficient control and prevention of the disease (Lindsay et al., 2019), which principally relies on comprehensive surveillance and analysis which are invaluable in tracking the trends of development and spread of antibiotic resistant typhoid pathogens (Tahir, 2019).

In many states of the world, efforts are being made in advancing the medical well-being of citizens indiscriminately, as a result, there is a need for efficient organization and installment of the limited funds and logistics available. Precautionary efforts usually yield capital-efficient results with an added benefit of indiscriminate beneficence in the population; however, these efforts can only be implemented in the presence of specific targets which cannot be properly identified without adequate information on risk factors for the disease (Wilson et al., 2012).

Precise factors which influence spread of typhoid are undeterminable, however, they will remain insignificant as long as proper water, sanitation, and disinfection processes are in place (Tallis, 2001). However, traditional and personal methods of preparing and managing consumable items, sanitation procedures, coupled with geographical variations and inadequate literacy regarding sanitation procedures (Tran et al., 2005), along with the social and structural setting a person lives in (Shohaimi et al., 2003), could expose members of a population to diverse variables which positively influence their exposures to *S. typhi*.

Extremely limited information is available on these variables that influence exposure to *S. typhi* in regions where the resulting infection is quite common, regardless of the significant effect of this disease on the population in those areas. On the other hand, many health survey studies on spread of typhoid in times of rapid occurrences of the disease revealed that people who frequently contact or process consumables were significant in creating rapid transmission of the pathogen. Nonetheless, a comprehension of the exposure variables that influence spread of this disease in regions where it is very common but not rapidly occurring is vital to control efforts because the information obtained during rapid occurrences can be said to be partial because such cases may have been due to a single variable or accident (Hosoglu et al., 2006).

This review is aimed at creating a collection of documented risk factors and control challenges for typhoid fever from studies carried out in various regions of the world, to provide adequate information which can reduce the knowledge gap that exists with regards to risk factors and control challenges for this disease.

Methods

A non-systematic narrative review to obtain scholarly publications from various geographical locations was employed to outline the risk factors and control challenges for typhoid fever. No comprehensive inclusion criteria was utilized for selecting the articles but when feasible only peer-reviewed articles were selected, however, the following keywords were used for the searches; typhoid epidemiology, typhoid occurrence, typhoid prevalence, typhoid incidence, typhoid determinants, typhoid risk, typhoid control challenge, and typhoid distribution, in the following databases: PubMed, Google Scholar, JSTOR, and Sciencedirect, all in English language, from 1997 to 2019 (Muresu et al., 2020).

RESULTS

Initially a total of 112 publications were selected for this study, however, based on abstracts and full texts, only 76 were used for this review, among which 25 were related to typhoid risk factors, 20 were related to antibiotic resistance in *S. typhi*, 16 were related to typhoid disease burden, 10 were related with challenges to typhoid control, and 5 were related to the pathophysiology of the *S. typhi*.

Typhoid Risk Factors

The results of this study revealed the following typhoid risk factors: contaminated water, contaminated food, contact with a typhoid carrier, contact with a typhoid patient, lack of proper handwashing, lack of vaccination, hot weather, mechanical vectors, occupation, and travel. These typhoid risk factors are specific elements or attributes of the physical and social surroundings that elevate the prospects that an individual will take part in hypothetically detrimental actions or be exposed to detrimental health effects that will lead this individual to get infected with *Salmonella typhi* (WHO, 2019).

Contaminated water

The occurrence of *S. typhi* infections can become quite common where ageing and improperly maintained water sources are most utilized. For example, reports from a study involving the Swat area in Pakistan State revealed that most of the population there utilize sources of water that have been existing for one to two decades with the most accessed been wells, followed by hand-operated pumps, springs, and open streams/rivers which have been responsible for significant occurrences of typhoid in that area (Khan et al., 2018). A report from an enquiry into a widespread occurrence of *S. typhi* infections in Kampala, Uganda in 2015 revealed consuming polluted unregistered publicly sold water along with untreated groundwater as factors that increased the risks of transmission of the pathogen to individuals in that area (Murphy et al., 2017).

Contaminated food

Individuals in large urban settlements were shown to be prone to occurrences of *S. typhi* from consumption of hawked consumable items which are a usual practice in south Asia (Ram et al., 2007). Regardless of little occurrences of *S. typhi* infections in America (USA), widespread occurrences of typhoid still emanate because of pollution of consumable items by ill people, and partly due to ingress of polluted consumable items from other nations. A widespread outburst of occurrences involving *S. typhi* infections was investigated in the north west part of the state of Oklahoma, USA in 2015, where reports revealed majority of the ill people resided in one area and all of them were present at a public gathering in which consumables were handed out, and some of the individuals probably touched someone that was subsequently established to be already typhoidal before coming to the gathering (Burnsed et al., 2019).

Contact with a typhoid carrier

Consuming items that have been polluted by faecal material of non-symptom-displaying carriers of *S. typhi* also represent an important source of typhoid transmission through the faecal-oral route (Dolecek, 2016). Approximately, five out of every 100 typhoidal individuals develop long-lasting carriage of the pathogens which are erratically egested along with faeces after the patient's recovery. Almost a quarter of individuals with long-lasting carriage of *S. typhi* in a society had never experienced any symptom of the disease, this also increases spread of the pathogen because these individuals will have no idea of what they are carrying and so will make no effort to get treated and hence will continue to shed the bacteria thereby infecting people around them (Harris & Brooks, 2012).

Contact with a typhoid patient

Another important variable which positively influences transmission of *S. typhi* and possible hospitalisation due to infection is interaction with an individual that is infected with the pathogen and is ill due to the disease (Luxemburger et al., 2001). The few numbers of typhoid pathogen cells required to initiate

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an infection, approximately 100 to 1000 cells, fewer requirement compared to other *Salmonella,* could be responsible for this simple mode of spread of the pathogen (van Seventer & Hochberg, 2016). In addition to this, interaction between individuals aids unhindered straight transmission of huge numbers of this typhoid bacterium (Ashurst et al., 2019).

Lack of proper hand washing

Proper discarding of faecal materials in addition to suitable cleaning of hands using detergents, disinfectants or a combination of both, present two of the main obstacles against spread of *S. typhi*, most importantly if they are employed post-interaction with faeces because fingers and human palms play important roles as transmitters of diseases through consumable items (Khan et al., 2012) especially if a cook has the disease or is a carrier (Sur et al., 2006). Failure to utilize detergents or disinfectants in cleaning hands in a region where *S. typhi* infections are very common can raise the chances of getting the disease up to thirtyfold (Velema et al., 1997), and up to threefold where the disease is not very common (Greenwell et al., 2013).

Lack of vaccination

Unimmunized individuals possess twice the probability of contracting *S. typhi* infection in relation with their immunized counterparts. A study on typhoid cases revealed that a large portion of individuals with the disease were found to be unimmunized as compared to the smaller group of cases whom had been immunized previously in Punjab, Pakistan (Rasul et al., 2017). Few members of a society that have not been immunised against typhoid usually gain some sort of indirect fortification resulting from them been intermixed with many people that have had the immunization, this kind of shielding is termed herd protection, and works by reducing the population of the pathogen that is in circulation and thus limiting the chances of acquiring infection by the unimmunized people (Chao et al., 2015).

Hot weather

Illness resulting from exposure to *S. typhi* could be influenced by changes in weather conditions. A rise in habit of drinking cold water, frozen beverages and some other domestically produced traditional beverages usually accompanies a rise in temperature of the environment, but unfortunately, a lot of such consumables were shown to be variables which positively influence spread of *S. typhi* due to its ability to survive in cold temperatures and the unhygienic methods involved in the production and handling of such consumables (Awofisayo-Okuyelu et al., 2018). An analysis involving risk factors for *S. typhi* transmission revealed that an increase of one degree Celsius in environmental temperature could be responsible for up to a fourteen percent rise in *S. typhi* infections in Dhaka, Bangladesh (Dewan et al., 2013).

Mechanical vectors

A study which analysed collections of *M. domestica* captured in health facilities and abattoirs in Iran reported that these insects harboured drug non-responsive bacteria which led to a conclusion about these insects been implicated significantly in transmission of these pathogens (Sarwar, 2015). *S. typhi* transmission could similarly result from exposure of consumable items to faecal material transported mechanically via the limbs of the housefly (Ommi et al., 2017).

Another analysis of a collection of more than five hundred *M. domestica* insects revealed that ninety-five of the flies harboured pathogenic bacteria including the typhoid pathogen in Iran (Vasan et al., 2008). The typhoid pathogen had likewise been recovered from *Periplaneta americana* (the American cockroach species), *Blattella germanica* (the

German cockroach species), and *Blatta orientalis* (the Oriental cockroach species), which also inertly spread the pathogen and can be found in homes and commercially active places (Mogasale et al., 2014).

Occupation

Occupation also plays a role in spread of typhoid, especially when achievable pre-emptive steps are ignored leading to accumulation of risks mainly by unhygienic practices and conditions. For example, frequency of deaths resulting from *S. typhi* infections were almost elevated 10-fold in trading sea farers of Britain when compared to other members of the society, mostly due to unsanitary conditions aboard ships and in seaports (Anthonj et al., 2019).

Also, individuals can contract *S. typhi* infections if they work in factories that collect and recycle used materials which include domestic or commercial wastes that may be contaminated with the pathogen (Behrman, 2011). Furthermore, elevated hazards of typhoid fever exist for individuals that work in processing or disposing infectious clinical items such as laboratory typhoid specimens (Mileno et al., 2019).

Travel

With respect to travelling as a variable that increases probability of contracting *S. typhi* infection, the most influential sub-variable is the location an individual is travelling to. Individuals travelling to South Asian nations, particularly, Bangladesh, India, and Pakistan, have the most significantly elevated risks of contracting *S. typhi* infections, followed by those travelling to countries in Northern Africa, Sub-Saharan Africa, South America, and the Middle East who are exposed to an average risk, and then lastly those travelling to Central America and the Caribbean who are at the least peril of contracting the disease (Mileno et al., 2019). Another identified cluster of travelling individuals at notable peril of contracting typhoid as a result of their travel are those visiting family members and friends because, usually, these people do not consider asking for guidance before embarking on the journey, they also do not adopt health precautions when mingling with their hosts or friends, and usually spend extended durations at such locations (Pitzer et al., 2018). The disease burdens associated with some of these typhoid risk factors are shown in table 1.

Table 1: Some typhoid risk factors and their associated burdens

Risk factor	Location	Time	Cases	Deaths	Citations
-Contaminated water	Dushanbe, Tajikistan	1st January – 30th June 1997	8901	95	Mermin et al. (2002)
	Nek Muhammad village, Karachi, Pakistan	October 2004	~ 300	3	Farooqui, Khan, & Kazmi (2009)
	Kampala, Uganda	2015	Outbreak	NA	Murphy et al. (2017)
	Kikwit, Democratic Republic of Congo (DRC)	2011-2012	~ 1430	17	Brainard et al. (2018)
	Kamalapur, Bangladesh	February 2003 - January 2004	41	NA	Ram et al. (2007)
-Contaminated food	Northwestern Oklahoma, United States of America (USA)	February 2015	38	None	Burnsed et al. (2019)
	Central Division, Fiji	2014 - 2017	279	NA	Prasad et al. (2018)
	Egypt	NA	477	NA	Sheded et al. (2018)
	Diyarbakir, Turkey	May 2001 – May 2003	64	NA	Hosoglu et al. (2006)

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	Kamalapur, Bangladesh	February 2003 - January 2004	16	NA	Ram et al. (2007)
-Contact with a typhoid carrier	USA	1960 - 1999	~ 593	4	Olsen et al. (2003)
	Barcelona, Spain	1988 - 1994	70	NA	Sohn et al. (1997)
	USA (Mary Mallon)	1906 - 1910	122	5	Marineli et al. (2013)
-Contact with a typhoid patient	Mekong Delta, Vietnam	May 1996 – July 1997	144	None	Sur et al. (2006)
	Kolkata, India	January – December 2004	5	None	Velema et al. (1997)
-Lack of proper hand washing	Kolkata, India	January – December 2004	17	None	Velema et al. (1997)
	Ujung Pandang, Indonesia	June – September 1991	22	NA	Gasem et al. (2001)
	Semarang, Indonesia	December 1992 – February 1994	76	NA	Rasul et al. (2017)
-Lack of vaccination	Gujrat, Punjab, Pakistan	May 2015 - June 2016	~ 248	NA	Srikantiah et al. (2007)
-*Helicobacter pylori* infection	South Delhi, India	November 1995 – October 1996	~ 28	NA	Bhan et al. (2002)
-Recent use of oral antimicrobials	Uzbekistan	July 2002	24	NA	Luby et al. (1998)
	Dhaka, Bangladesh	February 2003 - January 2004	7	NA	Ram et al. (2007)
	Karachi, Pakistan	July – October 1994	25	NA	Ayaz et al. (2005)
-Congestion	Diyarbakir, Turkey	May 2001 -May 2003	~ 19	NA	Cissé (2019)

KEY: NA = not available

Challenges to Typhoid Control

Unavailability of data

Efficient plans regarding delivery of typhoid interventions heavily rely on improved comprehension of time-based and location-based variations in the changing aspects of *S. typhi* spread, including the outbreak probability vs outbreak response plans, and where data to guide such comprehension is unavailable, it is imperative that alternative but possible steps be taken to use the limited available information or generate modelled information so as to guide verdicts for efficient dispatch and delivery of interventions against the disease, identify barriers to achieving control of this pathogen, guarantee comprehensive knowledge dissemination about the implications of this disease and the importance and advantages that will result from implementation of efficient interventions in regions where the disease is rampant (Carey et al., 2019).

Vaccine limitations

There are two vaccines against *S. typhi* infection which have been approved for global use, however, these vaccines are almost 30 years old and have certain limiting factors which include low efficiency, low number of protection years, and how old a person must be to be able to receive the immunization which are more than two years and more than 5 years for the ViPS (Vi capsular polysaccharide) and Ty21a (live attenuated Ty21a oral vaccine) respectively. However, there is hope that such limiting factors will be overcome by other comparatively recently developed vaccines. For example, a pilot test in Vietnam involving children aged between 2 to 5 yielded more than 90% effectiveness when the new VirEPA (recombinant exoprotein A of *Pseudomonas aeruginosa*) vaccine was used for immunization against *S. typhi* infection. Unfortunately, almost two decades after this test, the VirEPA typhoid

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vaccine had still not received approval for global use (MacFadden et al., 2016).

Diagnostic limitations

In many regions of the world where there is little or no data from hospital investigations or local surveys, it is usually exceedingly difficult to ascertain the actual burden resulting from typhoid fever infections. This problem has been exacerbated due to absence of cheap, precise, and fast investigative tests and processes, inconsistencies in diagnostic and reporting steps, and the presence of other fever-associated diseases like malaria in the host which give a false-positive result in some rapid typhoid fever diagnostic tests (Bentsi-Enchill & Pollard, 2018).

Without better diagnostic systems, it is almost impossible to formulate information regarding epidemiological factors and common strains of the pathogen which can be used to build evidence to support mindfulness and sway verdicts of authorities towards implementation of hospital-based, environmental, and social interventions against the disease including screening, documentation, and treatment of asymptomatic carriers (Steele et al., 2016). It is believed that due to incorrect diagnosis and subsequent unjustifiable treatment of *S. typhi* infections with antibiotics, individuals tend to develop multi-drug resistance to antibiotics used in conventional typhoid treatment (Felgner et al., 2017).

Economic conditions

Financial analyses have shown that efforts to achieve worldwide provision of safe drinkable water and proper sanitation costed nearly US$17.5 billion and US$35 billion respectively each year between 2010 to 2015, this brings into play the issue of practicability particularly in developing and underdeveloped nations. Bias in distribution, growing water shortage in certain places, rising urban development rates (Steele et al., 2016), and changing climatic conditions, have continued to create barriers to provision of safe water, proper sanitation, and advancement of infrastructure which are all aimed at controlling typhoid fever (Carey et al., 2019).

Lack of suitable animal models and human infection studies

Majority of the disease-causing mechanisms of the typhoid bacteria cannot be properly re-created outside the human body because this pathogen and its subsequently produced toxin affect only humans and as such studies into its mechanism of infection cannot be properly studied (Yang et al., 2018). Even though other alternative primate and mice subjects are available, both have their disadvantages when it comes to using them to study a disease that specifically infects only humans (Darton et al., 2014).

Increase in drug resistance

In parts of the world where *S. typhi* infections are prevalent, the key obstacle towards achieving effective control of this pathogen is its advancement in antibiotic non-responsiveness which has been progressing over the last four decades. Over the past two decades, fluoroquinolone resistance by *S. typhi* has been emerging and spreading in the presence of already established multidrug resistance (MDR) which has led to widespread utilization of newer third generation cephalosporin antibiotics and azithromycin which is subsequently leading to development of non-responsiveness towards them also, nonetheless, some other newer drugs could still be exploited but this effort can still not be achieved except with the generation of more data from clinical trials (Karkey et al., 2018). Some recorded cases of drug resistant *S. typhi* are shown in table 2.

Table 2: Some documented cases of antibiotic resistant *Salmonella typhi*

Year	Location	Isolates	Antibiotic resistance percentages	Citations
2018	Bangladesh	33	Azithromycin = 95% Resistance (R), Clindamycin = 100% R,	Ahsan & Rahman (2018)
2018	Abia, Nigeria	72	Amoxicillin = 86.1% R, Co-trimoxazole (TSM) = 72.2% R, Chloramphenicol = 56.9% R, Augmentin = 72.2% R,	Emmanuel & Emmanuel (2018)
2018	Nairobi, Kenya	287	MDR = 55.5%, Fluoroquinolones = 18.2% R, Cephalosporins = 15.4% R,	Kavai et al. (2018)
2017	Southern Pakistan	322	Ciprofloxacin = 62.5% R, Ceftriaxone = 20.7% R, Multi-drug resistant (MDR = 17%, Extensively drug-resistant (XDR) = 3.7%,	Tahir, 2019
Nov 2016 to Sep 2017	Sindh, Pakistan	339	XDR = 100%,	Klemm et al. (2018)
Nov 2016 to Dec 2017	Hyderabad, Pakistan	486	Ceftriaxone = 100% R	Qamar et al. (2018)
2008 to 2016	North-eastern Tanzania	129	Amoxicillin = 89.9% R, Chloramphenicol = 81% R, TSM = 92.1% R, MDR = 81%,	Msemo et al. (2019)
1993 to 2015	Lagos, Nigeria	NA	MDR = >80%,	Akinyemi et al. (2018)
Sep 2013 to May 2014	Luanda, Angola	14	TSM = 42.9% R, β-lactams = 35.7% R, Chloramphenicol = 7.1% R, Ciprofloxacin = 14.3% R,	Francisco et al. (2018)
2009 to 2014	Nairobi, Kenya	225	Ampicillin, Chloramphenicol, Co-trimoxazole, Tetracycline = 60.5 % R	Kavai & Kariuki (2019)
May 2012 to Sept 2013	Sylhet, Bangladesh		Cotrimoxazole = 97.14% R, Azithromycin = 95.29% R, Cefixime = 91.43% R, Tetracycline = 85.71% R, Ciprofloxacin = 77.14% R, Ceftriaxone = 68.57 % R,	Rahman (2015)
2002 to 2013	South India	1,905	Stable MDR,	Joshi et al. (2019)
1998 to 2012	Kolkata, India	164	MDR = 82.8%,	Das et al. (2017)
2011	Taiwan	49	First 2 strains ever with 100% R to ciprofloxacin	Lee et al. (2013)
Nov 2011 to Nov 2012	Bangladesh	70	MDR = 64.28%	Mannan et al. (2014)
2005 to 2009	Pondicherry, India	337	MDR = 22%, Nalidixic acid resistance (NAR) = 78%, Ciprofloxacin = 8% R,	Menezes et al. (2012)
2004 to 2007	Kenya	144	Ampicillin = 72% R, Chloramphenicol = 72% R, Cotrimoxazole = 70% R,	Mutai et al. (2018)

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2002 to 2007	Egypt, Uzbekistan, Pakistan, Qatar, Jordan, and Iraq	968	Iraq = 83% MDR, 92% reduced susceptibility to ciprofloxacin (RSC), Pakistan = 52% MDR, 47% RSC, Uzbekistan = 80% RSC, Qatar = 54% RSC	Rahman et al. (2014)

CONCLUSION

This review has highlighted ten typhoid risk factors and six challenges to typhoid control, which along with the escalating antibiotic resistance developments by the typhoid pathogen, will continue to pose serious threats to public health especially in developing and underdeveloped nations unless targeted and sustained health interventions are implemented or escalated.

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