**Chapter**

# Typhoid in Less Developed Countries: A Major Public Health Concern

*Tigist Gashaw and Abera Jambo*

## Abstract

Typhoid fever remains a major public health concern in less developed countries. The disease is transmitted through the consumption of food or water contaminated with feces containing Salmonella Typhi. *Salmonella* is a genus of the family *Enterobacteriaceae* with over 2450 species. Typhoid is more common in impoverished areas with unsafe drinking water sources and poor sanitation. These problems are further exacerbated by political instabilities, displacement, and war in the regions. Each year, 17.8 million cases of typhoid fever are reported in lower-income countries. Typhoid was expected to be most common in western Africa, followed by a few countries in Central, South, and Southeast Asia. In most cases, the incidence peaked between the ages of under 5 years. Recently, many *Salmonella* species had developed resistance to several antibiotics which call for serious prevention and control efforts that integrate several high-impact interventions targeting facilities and infrastructure, together with parallel efforts directed at effective strategies for use of typhoid conjugate vaccines. Hence, a multisector collaboration and approach from a different perspective have to be advocated for the containment of typhoid. The clinical and public health concerns and the strategies to stem the growing flows associated with typhoid are going to be discussed.

**Keywords:** typhoid, developing countries, antimicrobial resistance, typhoid conjugate vaccine, sanitation, hygiene

## 1. Introduction

Typhoid fever is an infection of the gastrointestinal tract, particularly the intestinal lumen, and it may involve the bloodstream [1]. Typhoid and paratyphoid fever are caused by gram-negative bacteria known as Salmonella typhi and *Salmonella Paratyphoid*, respectively, with the latter causing less severe disease, and they pose serious health problems to humans [2–4]. Eating contaminated food or drinking contaminated water is the main pathway through which these bacteria can spread [5, 6]. Typhoid fever is among the most common foodborne diseases and remains the major health problem in low-income countries while become declined in developed countries because of improved sanitation, safe food, and water [7–10].

### 1.1 Epidemiology of typhoid fever

Even if there is a drastic decrease in typhoid fever-related morbidity and mortality with improved living conditions and the introduction of antibiotics, the disease continues to be a public health problem in areas of Africa, the Americas, Southeast Asia, and the Western Pacific regions [11–13]. It is predicted that about 17.8 million cases of typhoid fever occur each year in low- and middle-income countries with Central Africa predicted to experience the highest incidence followed by Central, South, and Southeast Asia [14, 15].

It was also estimated that 14·3 million cases of typhoid and paratyphoid fevers occurred globally in 2017. Comparing global burden diseases (GBDs) super-regions, south Asia had the highest age-standardized incidence rate followed by Southeast Asia, western sub-Saharan Africa, eastern sub-Saharan Africa, and Oceania. Besides, South Asia had the largest number of cases, accounting for 71·8% of global cases followed by Southeast Asia, western sub-Saharan Africa, eastern sub-Saharan Africa, and East Asia as depicted in table below. Considering age, incidence rates were highest among children, peaking in 5–9 year ages. With 12.6% of cases occurred among children younger than 5 years and 55.9% occurred among children younger than 15 years [16].

Furthermore, it was estimated that 135·9 thousand deaths from typhoid and paratyphoid fever globally in which 85.9% were attributable to *S. typhi* in 2017 (**Table 1**). South Asia had showed the highest mortality rate with highest absolute of deaths 69.6% followed by sub-Saharan Africa super-region 15.9%, South Asia, East Asia, and Oceania super-region 12.3% of global death. In addition, mortality rates were highest among young children, with 17.2% of deaths occurred in younger 5 years and 59.3% under 15 years old. Considering sex, 74.0 thousand deaths occurred among males compared with 61.9% thousand death among females [16].

### 1.2 Clinical presentation and diagnostic consideration of typhoid fever

The clinical presentations of typhoid fever vary with the age of the patients as well as whether complications are present or absent [17]. Initially, patients may present with fever which is gradual in type and rises to 39–40°C at the end of the first week of disease onset [18]. Patients with typhoid fever present with gastrointestinal (GI) symptoms like nausea and vomiting, constipation, diarrhea, and abdominal pain [19, 20]. Patients may also present with non-GI symptoms like headache, skin rash, cough, and malaise [4]. Fever is the only frequent sign seen among under 5 years children unless the patient is presented with complications [19]. Nonspecific physical findings like soft and tender hepatosplenomegaly, distended abdomen, ascites, and diffuse/localized tenderness may also be noticed upon physical examination. Hepatitis and hepatomegaly are more common among children aged under 5 years, whereas constipation is common among adults [18, 21]. Some rare clinical features like bradycardia which may be secondary to high persistent fever, rose spots, and blanching erythematous maculopapular lesions on the trunk were also reported among patients with typhoid fever [22–24]. In the diagnosis of typhoid fever, in addition to the presenting symptoms, a culture test is considered [25].

### 1.3 Complications of typhoid fever

A severe form of the disease manifests in the second/third week of the illness with persistent fever, anemia, weight loss, increasing weakness, and persistent

| | Cases (thousands) | Incidence (per 100,000) | Death (typhoid fever) |
|---|---|---|---|
| Global | 14,321 (12540–16,337) | 197·8 (172·0–226·2) | 85·9% (77·7–91·9) |
| **Central Europe, Eastern Europe, and Central Asia** | | | |
| Central Asia | 0·1 (0·1–0·1) | 0·1 (0·1–0·1) | 48·9% (22·2–87·2) |
| Central Europe | 1·2 (0·9–1·5) | 0·7 (0·6–0·9) | 62·6% (47·0–80·1) |
| Eastern Europe | 1·1 (0·9–1·5) | 0·4 (0·3–0·5) | 41·8% (27·0–62·7) |
| **High income** | | | |
| Australasia | 0·0 (0·0 to 0·1) | 0·2 (0·1–0·2) | 39·2% (14·0–58·2) |
| High-income Asia Pacific | 0·7 (0·6 to 0·9) | 0·3 (0·2–0·3) | 34·1% (18·0–73·8) |
| High-income North America | 4·1 (3·2 to 5·3) | 0·9 (0·7–1·2) | 18·6% (6·2–30·5) |
| Southern Latin America | 0·5 (0·4 to 0·6) | 0·7 (0·5–0·9) | 97·7% (92·8–99·0) |
| Western Europe | 1·3 (1·0 to 1·6) | 0·3 (0·2–0·4) | 84·3% (77·1–96·4) |
| **Latin America and Caribbean** | | | |
| Andean Latin America | 0·9 (0·7–1·1) | 1·5 (1·2–2·0) | 98·8% (97·8–99·4) |
| Caribbean | 2·5 (2·1–3·0) | 5·7 (4·7–6·7) | 56·3% (40·7–70·4) |
| Central Latin America | 20·0 (16·6–24·6) | 8·2 (6·9–10·2) | 98·3% (94·3–99·6) |
| Tropical Latin America | 4·3 (3·3–5·5) | 1·9 (1·5–2·4) | 98·7% (97·6–99·3) |
| North Africa and Middle East | 246·6 (210·8–286·3) | 39·3 (33·7–45·6) | 98·4% (97·2–99·2) |
| South Asia | 10,286 (9002–11,738) | 549·2 (480·7–625·4) | 83·4% (73·9–90·3) |
| **Southeast Asia, East Asia, and Oceania** | | | |
| East Asia | 586·6 (553·8–624·0) | 51·0 (47·3–55·1) | 76·9% (65·3–86·0) |
| Oceania | 20·5 (17·0–24·7) | 144·3 (121·5–170·4) | 87·2% (79·4–92·9) |
| Southeast Asia | 1414·4 (1247·9 to 1592·9) | 219·8 (192·9–249·1) | 94·5% (90·4–97·0) |
| **Sub-Saharan Africa** | | | |
| Central sub-Saharan Africa | 122·4 (100·2–149·1) | 81·4 (68·8–95·8) | 98·5% (97·4–99·2) |
| Eastern sub-Saharan Africa | 739·5 (627·6–869·7) | 151·9 (132·0–174·6) | 99·1% (98·3–99·5 |
| Southern sub-Saharan Africa | 1·9 (1·7–2·1) | 2·3 (2·0–2·6) | 95·5% (92·3–97·6) |
| Western sub-Saharan Africa | 866·1(719·7–1039·6) | 161·1(138·1–187·3) | 84·8% (76·2–91·4) |

**Table 1.**
*Global and regional numbers of cases, incidence and deaths by year 2017 for typhoid and paratyphoid fevers [16].*

GI manifestations (vomiting) [18]. Unless treated early, typhoid fever may also lead to encephalopathy, nephritis, GI bleeding, and hepatitis [26–28]. So, early initiation of appropriate treatment helps to reduce the chance of developing such complications.

## 2. Factors associated with typhoid fever

Different factors were associated with typhoid fever including individual, environmental, and socioeconomic-related factors. Accordingly, individual-related factors like a decreased gastric acid barrier and taking medications that decrease gastric acidity and a history of *Helicobacter pylori* infection increase the chance of acquiring typhoid fever [10]. In addition to this, poor hygiene practices in an individual as well as in the community level increase the likelihood of acquiring the disease [29]. Among environmental factors, the risk of acquiring typhoid fever is associated with being exposed to solid waste disposal on the field, nearby open sewers and contaminated water bodies, being a resident of low elevation areas, and the rainy season [29–31]. Different socioeconomic factors also increase the risk of acquiring typhoid fever. Those being user of spring and river water, and use of pit latrine, as well as individuals with low income, were more likely to get infected [32–34].

## 3. Impacts of typhoid fever

Typhoid fever is the result of a human host-restricted *Salmonella* enteric serotype *Typhi* infection that causes enteric fever [35]. Antibiotics are commonly used to treat typhoid fever, and early initiation of effective antimicrobial therapy has been shown to reduce disease duration as well as the risk of complications and death [36]. Clinicians may prescribe antibiotics to patients who do not have a confirmed diagnosis, based on clinical suspicion, due to the high risk of morbidity and mortality if untreated [37]. Large surveillance studies from Asia and Africa, on the other hand, show that only 1–4% of people with suspected typhoid have culture-confirmed typhoid [38], implying that unnecessary antibiotics are commonly used. Empiric antibiotic treatment has been shown to increase selection pressure on *Salmonella Typhi* (*S. Typhi*) [39]. As a result, with rising rates of treatment failure, antibiotic resistance has emerged as a major threat to typhoid treatment [40–42].

Different researchers are witnessing the full-blown resistance development toward former first-line antimicrobials against typhoid fever [43–45]. A similar pattern of resistance is also increasing toward the fluoroquinolones (ciprofloxacin) accounting for up to 80% of isolates [43, 45, 46]. Moreover, the backups cephalosporin (ceftriaxone and cefotaxime) is also in question marking up to 50% resistance in some specific areas [41]. Fortunately, the susceptibility of Azithromycin has been retained in many areas [46]. Though the potency of Carbapenems is still present [46], there is emerging evidence of resistance to Morepenem in a few findings [41]. In some areas, patients were wrongly diagnosed and treated for enteric fever by the Widal test. Rapid tests with better sensitivity and specificity are needed for the diagnosis of enteric fever [44]. Consequently, the magnitude of multiple and extended drug resistances is increasing in developing countries [47].

Multidrug resistance (MDR) refers to resistance to first-line antibiotics chloramphenicol, co-trimoxazole (trimethoprim-sulfamethoxazole), and ampicillin. In *S. Typhi,* complex MDR elements can be found on self-transmissible plasmids encoding an antibiotic resistance gene cassette or incorporated into the chromosome [48, 49]. While antibiotic selection keeps resistance genes on plasmids, there appears to be competition between plasmids encoding the same resistance trait [50]. Because of the spread of the specific H58 lineage across Asian and African countries, MDR *S. Typhi* has become common in many low-income countries, particularly in South and Southeast Asia [51–53]. Antimicrobial susceptibility patterns, like illness incidence, also vary spatially [54].

## 4. Preventions

Typhoid fever is a preventable disease. However, it continues to affect many populations across the globe. The biggest illness burden is seen in regions with low socioeconomic development, limited access to clean water, sewage and water management systems, poor sanitation standards, and other social risk factors such as population displacement, armed conflict, and natural disasters [55]. Hence, public health and clinical measures, which include improvements in water quality and sanitation [35], the deployment of *S. Typhi* vaccination and an informed choice of treatment must be implemented [56]. Reporting antimicrobial susceptibility testing is also imperative to facilitate evidence-based policy and practice to avert drug-resistant [52].

### 4.1 Vaccine

There are several vaccines available for the prevention of typhoid, the choice of which will include factors such as the local availability and age of the intended recipient. The World Health Organization (WHO) recommends the programmatic use of typhoid vaccines for the control of typhoid fever [57]. The three typhoid vaccines now in use globally are the unconjugated polysaccharide vaccine (Vi-PS), and the older generation typhoid conjugate vaccine (TCV) containing the Vi-polysaccharide antigen, and vaccination based on the injection of oral live attenuated *Salmonella strain* Ty21a [58]. TCV is the preferred formulation at the moment due to its immunological properties, wider application (can be given to infants as young as 6 months), and longer-lasting protection after a single dose. The TCV formulation has addressed some of the issues that previously hampered the effectiveness of both polysaccharide and live vaccines [59]. To stimulate the immune system more strongly, the *S. Typhi* Vi-polysaccharide is coupled to a protein in this formulation.

The Vi-TT and Vi-CRM197 formulations are the first typhoid vaccines approved for use in children under the age of 2 years, and several TCVs have been licensed on a national scale [60]. They are WHO-approved for use in infants as young as 6 months old [61]. Because of the high number of young children who contract typhoid fever, this approval was significant. The WHO recommends giving TCVs to children as a single dose at 9 months of age or in their second year of life in typhoid fever-endemic countries [57, 62].

#### *4.1.1 Challenges, opportunities, and ways forward*

Because typhoid is endemic in low-income countries, the greatest demand for vaccines is expected to come from the public sector, where financial incentives for vaccine manufacturers are limited. It will be difficult to keep manufacturers interested in TCV production and even more difficult to generate interest in the development of newer generation vaccine candidates [63]. Vaccine introduction and programmatic cost for vaccination are other burdens. Besides, the lack of sufficient diagnosis as well as surveillance data on disease pathogenesis [64], drug susceptibility, and typhoid vaccine effectiveness further challenged these regions [65].

Fortunately, recent finding from clinical studies in Africa, Malawi, is starting to sparkle a light on TCV effectiveness [66]. Besides, Liberia becomes the first country in Africa to introduce TCV with a weeklong campaign to reach more than 1.9 million children aged 9 months to younger than 15 years old. After the campaign, the country determines to integrate TCV into the routine immunization program for all children at 9 months old [67].

Vaccinations must compete for funding within health ministry's alongside other health objectives because they typically provide a good return on investment. This is especially true if the total public health benefits of a vaccine have been calculated [68]. In the case of typhoid vaccines, this would include indirect protection of those who have not received the vaccine, a reduction in antibiotic use, and a reduction in the development of antibiotic-resistant organisms [69]. Moreover, limiting health inequities and the moral capital the vaccines generate, decreasing outbreaks and the health care delivery distortions, and minimizing economic consequences from the loss of business or tourism when an outbreak occurs are all factors that will reduce the risk of household poverty as a result of the cost of treating typhoid [55, 70].

### 4.2 Water, sanitation, and hygiene

Water, sanitation, and hygiene (WASH) are critical for human health. Despite this, over 884 million people worldwide lack access to safe drinking water. Almost 2.4 billion people do not have access to even the most basic sanitary facilities. Many people practice open defecation, endangering the safety of drinking water and personal water supplies. Babies and young children are more likely to die if they do not have access to safe drinking water. Many diarrheal illnesses are caused by contaminated water and poor sanitation. These conditions can lead to the deadly diseases typhoid fever and cholera. Poor WASH conditions are also linked to new issues such as drug-resistant typhoid fever [71, 72].

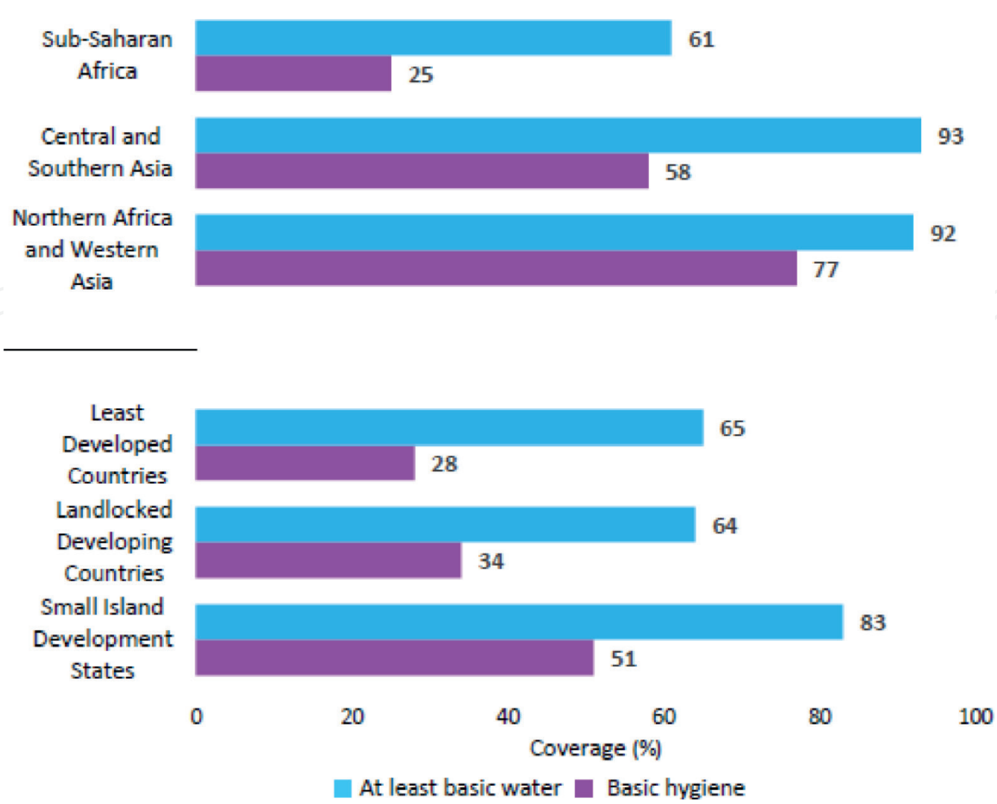


**Figure 1.**
*Access to at least basic water services and hygiene services at home for regions with available national representative data, SDG regions, and other regional grouping 2017 [73].*

Five years into the sustainable development goals (SDGs), the world is still on track to miss SDG target 6 (access to safe water and sanitation). To achieve universal coverage, current rates of advancement in properly managed drinking water services, securely managed sanitation services, and basic hygiene services must be quadrupled by 2030. Least-developed countries (LDCs) still have the most work to do, and accelerating progress in volatile environments will be especially difficult. Many more countries are struggling to provide services to their poor and vulnerable citizens, who are particularly at risk of being left behind (**Figure 1**) [73, 74].

Though international organizations and programs have been attempting to improve infrastructure as well as access to better sanitation and hygiene services focusing on schools [75, 76], it remained to be a key area of intervention [77] in reducing typhoid risk among children. Besides, insufficient funding and budgeting have been cited as major barriers to successfully integrating and maintaining WASH programs in school settings [78]. Involving the community by increasing user responsibility for program management and maintenance was one of the most crucial strategies to improve sustainability once funders or private financiers were no longer involved. By promoting community involvement, it may be simpler to make use of local resources, develop local WASH capacity, and guarantee user satisfaction [78, 79]. A significant reduction in typhoid risk has also been linked to the implementation of TCV programs and practical, culturally relevant family WASH practices [80].

## 5. Conclusions

A multidisciplinary strategy of public health based on personal protection and infrastructure interventions is needed. As typhoid vaccines do not offer complete protection, safe water, sanitation, and hygiene interventions are critical to preventing the spread of typhoid. Other efforts might be directed toward effective treatment options, to provide care as early as possible to achieve better outcomes. Additionally, as there is often limited awareness and knowledge of infectious diseases in affected populations, hence, education and community engagement should be considered.

## Conflict of interest

The authors declare no conflict of interest.

## Acronyms and abbreviations

| | |
|---|---|
| *S. Typhi* | *Salmonella Typhi* |
| GBD | global burden diseases |
| MDR | multidrug resistance |
| GI | gastrointestinal |
| TCV | typhoid conjugate vaccine |
| WASH | water, sanitation, and hygiene |
| SDGs | sustainable development goals |
| WHO | World Health Organization |

**Author details**

Tigist Gashaw[1]* and Abera Jambo[2]

1 Department of Pharmacology and Toxicology, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

2 Clinical Pharmacy Department, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

*Address all correspondence to: yekalabel@gmail.com

## References

[1] Sheikh A, Charles RC, Sharmeen N, Rollins SM, Harris JB, Bhuiyan MS, et al. In vivo expression of salmonella enterica serotype Typhi genes in the blood of patients with typhoid fever in Bangladesh. PLoS Neglected Tropical Diseases. 2011;**5**(12):e1419

[2] Harris JB, Brooks WA. Typhoid and Paratyphoid (Enteric) Fever. Hunter's Tropical Medicine and Emerging Infectious Diseases. Amsterdam, Netherlands: Elsevier; 2020. pp. 608-616

[3] Kuijpers LM, Phe T, Veng CH, Lim K, Ieng S, Kham C, et al. The clinical and microbiological characteristics of enteric fever in Cambodia, 2008-2015. PLoS Neglected Tropical Diseases. 2017;**11**(9):e0005964

[4] Habte L, Tadesse E, Ferede G, Amsalu A. Typhoid fever: Clinical presentation and associated factors in febrile patients visiting Shashemene referral hospital, southern Ethiopia. BMC Research Notes. 2018;**11**(1):1-6

[5] Ligon BL, editor. Infectious diseases that pose specific challenges after natural disasters: A review. In: Seminars in Pediatric Infectious Diseases. Amsterdam, Netherlands: Elsevier; 2006

[6] Ashbolt NJ. Microbial contamination of drinking water and disease outcomes in developing regions. Toxicology. 2004;**198**(1-3):229-238

[7] Musoke D, Namata C, Lubega GB, Niyongabo F, Gonza J, Chidziwisano K, et al. The role of environmental health in preventing antimicrobial resistance in low- and middle-income countries. Environmental Health and Preventive Medicine. 2021;**26**(1):100

[8] Eng S-K, Pusparajah P, Ab Mutalib N-S, Ser H-L, Chan K-G, Lee L-H. Salmonella: A review on pathogenesis, epidemiology and antibiotic resistance. Frontiers in Life Science. 2015;**8**(3):284-293

[9] Faour-Klingbeil D, Todd CD, E. Prevention and control of foodborne diseases in middle-east north African countries: Review of national control systems. International Journal of Environmental Research and Public Health. 2020;**17**(1):70

[10] Manesh A, Meltzer E, Jin C, Britto C, Deodhar D, Radha S, et al. Typhoid and paratyphoid fever: A clinical seminar. Journal of Travel Medicine. 2021;**28**(3):taab012

[11] Kothari A, Pruthi A, Chugh TD. The burden of enteric fever. The Journal of Infection in Developing Countries. 2008;**2**(04):253-259

[12] Buckle GC, Walker CLF, Black RE. Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. Journal of global health. 2012;**2**(1):-010401

[13] Otegbayo J. Typhoid fever: The challenges of medical management. Annals of Ibadan Postgraduate Medicine. 2005;**3**(1):52-54

[14] Carvalho MS, Antillón M, Warren JL, Crawford FW, Weinberger DM, Kürüm E, et al. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLOS Neglected Tropical Diseases. 2017;**11**(2):e0005376

[15] Collaborators GTaP. The global burden of typhoid and paratyphoid

fevers: A systematic analysis for the global burden of disease study 2017. The Lancet Infectious Diseases. 2019;**19**:369-381

[16] Stanaway JD, Reiner RC, Blacker BF, Goldberg EM, Khalil IA, Troeger CE, et al. The global burden of typhoid and paratyphoid fevers: A systematic analysis for the global burden of disease study 2017. The Lancet Infectious Diseases. 2019;**19**(4):369-381

[17] Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. The Lancet infectious diseases. 2005;**5**(10):623-628

[18] Basnyat B, Qamar FN, Rupali P, Ahmed T, Parry CM. Enteric fever. BMJ. 2021;**372**:n437

[19] Basnyat B. Tackling typhoid fever burden in South Asia. The Lancet Global Health. 2022;**10**(7):e932-e9e3

[20] Jamil B, Lashari I, Bhatti S, Hasan RS. Enteric fever in adult patients: Clinical features, outcome and antibiotic susceptibility patterns. Infectious Disease Journal of Pakistan. 2004;**13**:68-72

[21] Balter S. Typhoid Fever, Acute and Carrier. Acute Communicable Disease Control 2016 Annual Morbidity Report. Los Angeles: CDC; 2016

[22] Lee B, Rose E. Other Potentially Life-Threatening Conditions with Mucocutaneous Findings (Leptospirosis, Typhoid Fever, Dengue, Diphtheria, Murine Typhus): Life-Threatening Rashes. Vol. 12. The Capital Region of Denmark: Springer, Cham; 2018. pp. 319-347. DOI: 10.1007/978-3-319-75623-3_23

[23] Kang JH. Febrile illness with skin rashes. Infection & Chemotherapy. 2015;**47**(3):155-166

[24] Lasheen RA, ElTohamy A, Salaheldin EO. MIS-C frenzy: The importance of considering a broad differential diagnosis. SAGE Open Medical Case Reports. 2022;**10**:1-5

[25] Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. Cochrane Database of Systematic Reviews. 2017;**5**:CD008892

[26] Pramoolsinsap C, Viranuvatti V. Salmonella hepatitis. Journal of Gastroenterology and Hepatology. 1998;**13**(7):745-750

[27] Anand AC, Garg HK. Approach to clinical syndrome of jaundice and encephalopathy in tropics. Journal of Clinical and Experimental Hepatology. 2015;**5**:S116-SS30

[28] Azmatullah A, Qamar FN, Thaver D, Zaidi AK, Bhutta ZA. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. Journal of Global Health. 2015;**5**(2):020407

[29] Akwa TE, Nguimbous SP. Investigation of typhoid fever and their associated risk factors in children attending "Deo Gratias" Hospital in Douala, Littoral, Cameroon. European Journal of Medical and Educational Technologies. 2021;**14**(2):em2107

[30] Dewan AM, Corner R, Hashizume M, Ongee ET. Typhoid fever and its association with environmental factors in the Dhaka metropolitan area of Bangladesh: A spatial and time-series approach. PLoS Neglected Tropical Diseases. 2013;**7**(1):e1998

[31] Baker S, Holt KE, Clements AC, Karkey A, Arjyal A, Boni MF, et al. Combined high-resolution genotyping and geospatial analysis reveals modes of endemic urban typhoid fever transmission. Open Biology. 2011;**1**(2):110008

[32] Irda Sari SY, Sunjaya DK, Shimizu-Furusawa H, Watanabe C, Raksanagara AS. Water sources quality in urban slum settlement along the contaminated river basin in Indonesia: Application of quantitative microbial risk assessment. Journal of Environmental and Public Health. 2018;**2018**:3806537

[33] Hamner S, Tripathi A, Mishra RK, Bouskill N, Broadaway SC, Pyle BH, et al. The role of water use patterns and sewage pollution in incidence of water-borne/enteric diseases along the Ganges River in Varanasi, India. International Journal of Environmental Health Research. 2006;**16**(2):113-132

[34] Dungumaro EW. Socioeconomic differentials and availability of domestic water in South Africa. Physics and Chemistry of the Earth, Parts A/B/C. 2007;**32**(15-18):1141-1147

[35] Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, et al. Extensively drug-resistant (XDR) typhoid: Evolution, prevention, and its management. BioMed Research International. 2020;**2020**:6432580

[36] Diniz-Santos DR, Silva LR, Silva N. Antibiotics for the empirical treatment of acute infectious diarrhea in children. Brazilian Journal of Infectious Diseases. 2006;**10**:217-227

[37] Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Ralph R. Typhoid fever: Issues in laboratory detection, treatment options & concerns in management in developing countries. Future science OA. 2018;**4**(6):FSO312

[38] Andrews JR, Baker S, Marks F, Alsan M, Garrett D, Gellin BG, et al. Typhoid conjugate vaccines: A new tool in the fight against antimicrobial resistance. The Lancet Infectious Diseases. 2019;**19**(1):e26-e30

[39] Tatavarthy A, Luna VA, Amuso PT. How multidrug resistance in typhoid fever affects treatment options. Annals of the New York Academy of Sciences. 2014;**1323**(1):76-90

[40] Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive salmonella infections. Clinical microbiology reviews. 2015;**28**(4):901-937

[41] Shah SAA, Nadeem M, Syed SA, Abidi STF, Khan N, Bano N. Antimicrobial sensitivity pattern of salmonella Typhi: Emergence of resistant strains. Cureus. 2020;**12**(11):e11778

[42] Sartelli M, Weber DG, Ruppé E, Bassetti M, Wright BJ, Ansaloni L, et al. Antimicrobials: A global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World journal of emergency surgery. 2016;**11**(1):1-32

[43] Mutai WC, Muigai AW, Waiyaki P, Kariuki S. Multi-drug resistant salmonella enterica serovar Typhi isolates with reduced susceptibility to ciprofloxacin in Kenya. BMC Microbiology. 2018;**18**(1):1-5

[44] Deksissa T, Gebremedhin EZ. A cross-sectional study of enteric fever among febrile patients at ambo hospital: Prevalence, risk factors, comparison of Widal test and stool culture and antimicrobials susceptibility pattern of isolates. BMC Infectious Diseases. 2019;**19**(1):1-12

[45] Mashe T, Gudza-Mugabe M, Tarupiwa A, Munemo E, Mtapuri-Zinyowera S, Smouse SL, et al. Laboratory characterisation of salmonella enterica serotype Typhi

isolates from Zimbabwe, 2009-2017. BMC Infectious Diseases. 2019;**19**(1):1-9

[46] Hughes MJ, Birhane MG, Dorough L, Reynolds JL, Caidi H, Tagg KA, et al. Extensively Drug-Resistant Typhoid Fever in the United States. Open Forum Infectious Diseases. US: Oxford University Press; 2021

[47] Butt MH, Saleem A, Javed SO, Ullah I, Rehman MU, Islam N, et al. Rising XDR-typhoid fever cases in Pakistan: Are we heading Back to the pre-antibiotic era? Frontiers in Public Health. 2022;**9**:794868

[48] Duy PT, Nguyen TNT, Thuy DV, Alcock F, Boinett C, Thanh HND, et al. Ciprofloxacin facilitates the transfer of XDR plasmids from commensal E. coli into epidemic fluoroquinolone-resistant Shigella sonnei. bioRxiv. 2019:767251 [Preprint]

[49] Sarwar Y, Ali A, Haque A, Haque A. Current status of antimicrobial resistance in enteric bacterial pathogens. Frontiers in Clinical Drug Research: Anti-Infectives. 2014;**1**:263

[50] Vogwill T, MacLean RC. The genetic basis of the fitness costs of antimicrobial resistance: A meta-analysis approach. Evolutionary Applications. 2015;**8**(3):284-295

[51] Azhar AB, Khalid A, Shah S. The implications of extensive drug-resistant typhoid fever: A case report. Cureus. 2019;**11**(6):e5032

[52] Browne AJ, Kashef Hamadani BH, Kumaran EA, Rao P, Longbottom J, Harriss E, et al. Drug-resistant enteric fever worldwide, 1990 to 2018: A systematic review and meta-analysis. BMC Medicine. 2020;**18**(1):1-22

[53] Masuet-Aumatell C, Atouguia J. Typhoid fever infection–antibiotic resistance and vaccination strategies: A narrative review. Travel Medicine and Infectious Disease. 2021;**40**:101946

[54] Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R. Global geographic trends in antimicrobial resistance: The role of international travel. Journal of Travel Medicine. 2019;**26**(8):taz036

[55] Khan MI, Franco-Paredes C, Sahastrabuddhe S, Ochiai RL, Mogasale V, Gessner BD. Barriers to typhoid fever vaccine access in endemic countries. Research and Reports in Tropical Medicine. 2017;**8**:37

[56] Parry CM, Ribeiro I, Walia K, Rupali P, Baker S, Basnyat B. Multidrug resistant enteric fever in South Asia: Unmet medical needs and opportunities. BMJ. 2019;**364**:k5322

[57] WHO. Typhoid vaccines: WHO position paper–march 2018. Weekly Epidemiological Record. 2018;**93**:477-500

[58] Emergent BioSolutions U. Vivotif-Summary of Product Characteristics (SmPC)-(Emc). London: Emergent BioSolutions UK; 2018

[59] Neuzil KM, Pollard AJ, Marfin AA. Introduction of typhoid conjugate vaccines in Africa and Asia. Clinical Infectious Diseases. 2019;**68**(Supplement_1):S27-S30

[60] Sahastrabuddhe S, Saluja T. Overview of the typhoid conjugate vaccine pipeline: Current status and future plans. Clinical Infectious Diseases. 2019;**68**(Supplement_1):S22-SS6

[61] Lau CL, Streeton CL, David MC, Sly PD, Mills DJ. The tolerability of a combined hepatitis a and typhoid vaccine in children aged 2-16 years: An observational study. Journal of Travel Medicine. 2016;**23**(2):tav023

[62] Bentsi-Enchill AD, Hombach J. Revised global typhoid vaccination policy. Clinical Infectious Diseases. 2019;**68**(Supplement_1):S31-SS3

[63] Syed KA, Saluja T, Cho H, Hsiao A, Shaikh H, Wartel TA, et al. Review on the recent advances on typhoid vaccine development and challenges ahead. Clinical Infectious Diseases. 2020;**71**(Supplement_2):S141-SS50

[64] Yang Y-A, Chong A, Song J. Why is eradicating typhoid fever so challenging: Implications for vaccine and therapeutic design. Vaccine. 2018;**6**(3):45

[65] Venkatesan P. A trial of a typhoid conjugate vaccine in children in Malawi. The Lancet Microbe. 2021;**2**(12):e654

[66] Patel PD, Patel P, Liang Y, Meiring JE, Misiri T, Mwakiseghile F, et al. Safety and efficacy of a typhoid conjugate vaccine in Malawian children. New England Journal of Medicine. 2021;**385**(12):1104-1115

[67] Birkhold M, Mwisongo A, Pollard AJ, Neuzil KM. Typhoid conjugate vaccine in Africa and Asia: Status of clinical evaluation and vaccine introduction. The Journal of Infectious Diseases. 2021;**224**:S781-S787

[68] Shakya M, Neuzil KM, Pollard AJ. Prospects of future typhoid and paratyphoid vaccines in endemic countries. The Journal of Infectious Diseases. 2021;**224**(Supplement_7):S770-S7S4

[69] Saha SK, Tabassum N, Saha S. Typhoid conjugate vaccine: An urgent tool to combat typhoid and tackle antimicrobial resistance. The Journal of Infectious Diseases. 2021;**224**(Supplement_7):S788-SS91

[70] Steele AD, Carey ME, Kumar S, MacLennan CA, Ma L-F, Diaz Z, et al. Typhoid conjugate vaccines and enteric fever control: Where to next? Clinical Infectious Diseases. 2020;**71**(Supplement_2):S185-SS90

[71] CDC. Assessing Access to Water & Sanitation. Obtenido de Centers for Disease Control and Prevention. USA: CDC; 2017

[72] Bangert M, Molyneux DH, Lindsay SW, Fitzpatrick C, Engels D. The cross-cutting contribution of the end of neglected tropical diseases to the sustainable development goals. Infectious Diseases of Poverty. 2017;**6**(1):1-20

[73] WHO. Progress on Household Drinking Water, Sanitation and Hygiene 2000-2020: Five Years into the SDGs. Geneva: WHO; 2021

[74] WHO. Progress on Household Drinking Water, Sanitation and Hygiene 2000-2017: Special Focus on Inequalities. New York: World Health Organization; 2019

[75] World Health Organization. Achieving Quality Universal Health Coverage through Better Water, Sanitation and Hygiene Services in Health Care Facilities. Geneva: WHO; 2017

[76] IRC U. Towards Effective Programming for WASH in Schools: A Manual on Scaling up Programmes for Water, Sanitation and Hygiene in Schools. Delft, The Netherlands: IRC International Water and Sanitation Centre; 2007

[77] Seid H, Kumie A. The status of school sanitation facilities in some selected primary and secondary schools in Dessie City Administration, south Wello zone, Amhara region. Ethiopian Journal of Health Development. 2013;**27**(1):80-84

[78] McGinnis SM, McKeon T, Desai R, Ejelonu A, Laskowski S, Murphy HM. A

systematic review: Costing and financing of water, sanitation, and hygiene (WASH) in schools. International journal of Environmental Research and Public Health. 2017;**14**(4):442

[79] Alexander KT, Zulaika G, Nyothach E, Oduor C, Mason L, Obor D, et al. Do water, sanitation and hygiene conditions in primary schools consistently support schoolgirls' menstrual needs? A longitudinal study in rural western Kenya. International Journal of Environmental Research and Public Health. 2018;**15**(8):1682

[80] Tadesse BT, Khanam F, Ahmed F, Im J, Islam M, Kim DR, et al. Prevention of typhoid by vi conjugate vaccine and achievable improvements in household WASH: Evidence from a cluster-randomized trial in Dhaka, Bangladesh. Clinical Infectious Diseases. 2022;**74**:ciac289