

UPDATE ON TYPHOID FEVER: AN ONGOING THREAT TO PUBLIC HEALTH

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ABSTRACT: Typhoid fever is a bacterial infection caused by the gram-negative bacterium *Salmonella enterica* subspecies *Serovar typhi*, transmitted mainly by contaminated water or food. Lack of access to safe drinking water and adequate sanitation in areas with poor hygiene conditions is a determining factor for the spread of the disease, making it more prevalent in developing countries. Prevention is essential to control typhoid fever, and measures such as vaccination, improvement of sanitary conditions and awareness campaigns on personal hygiene and food safety are key to reduce its incidence. Proper treatment with antibiotics is crucial to avoid serious complications. Antibiotic resistance has become an increasing challenge in the treatment of typhoid fever, highlighting the need for research and alternative strategies. This review aims to provide information on the epidemiology, diagnosis of typhoid fever and an update on novel medications used to prevent typhoid fever in developing countries.

Keywords: Typhoid fever. *Salmonella typhi*. Hygiene. Global Health.

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INTRODUCTION

Typhoid fever is a bacterial infection caused by the gram-negative bacterium *Salmonella enterica* subspecies *Serovar typhi*. It is contracted by consuming food or water contaminated by fecal or urinal matter containing *S. typhi*.^[1,2,3] with the exception of *S. paratyphi* and *S. Choleraesuis*, the rod-shaped, flagellated, and facultative anaerobic *S. typhi* can metabolize nutrients by respiratory and fermentative pathways referred to as chemoorganotrophic, producing hydrogen sulfide, and most do not ferment lactose.^[2]

The main sources of infection are contaminated feces and urine from infected persons, with contaminated water, poorly sterilized food and flies serving as the important vehicles of transmission, which can be classified as waterborne or foodborne causes of this gastrointestinal infection. The disease's onset and severity mostly determined by the organism's pathogenicity, virulence and the infecting dose.^[4]

Humans are host reservoirs for *S. typhi* which has a limited ability to multiply outside of the human host, although it can survive in the environment for extended periods of time but cannot multiply in contaminated food and water sources.^[5] Upon infection by the *S. typhi*, a person develops typhoid fever characterized by prolonged high fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhea.^[6] The *S. typhi* bacteria is shed by a convalescent carrier for 3-12 months after start of the illness. If the individual is not treated, he or she may have intestinal, neuropsychiatric, and other complications.^[7]

To safeguard the public against the disease, control measures such as early diagnosis, surveillance, and vaccination should be put in place. Likewise, sanitation and hygiene also play an essential role in lowering cases or eradicating disease.^[4] This review aims to provide information on the epidemiology, diagnosis of typhoid fever and an update on novel medications used to prevent typhoid fever in developing countries.

Epidemiology

Around the world in 2019, approximately 9.2 million cases and 110,000 deaths from *S. typhi* were reported, with children under the age of five being most at risk of infection.^[8] Southeast Asia had the greatest prevalence of typhoid fever at 306/100,000 in habitants, with the South Asian countries of Pakistan and Nepal having a high incidence of typhoid fever at over $\geq 100/100,000$ population.

Similarly, the Eastern Mediterranean region, Indonesia, and Samoa in Oceania reported a $\geq 100/100,000$ population incidence of typhoid fever. ^[8-10] In 2022, 14,056 cases of typhoid fever were reported in the Philippines. In other parts of the world, however, typhoid fever incidence rates vary. These incidence rates range to from less than 0.1/100,000 cases per year in Central Europe and North America to less than 10/100,000 in some African nations such as Liberia to $\geq 100/100,000$ inhabitants in Zimbabwe. ^[7-10]

In 2009, 303/100,000 instances were detected in Mozambique and Malawi, while in 2015, 10 cases were diagnosed out of 99 suspected cases, resulting in a 10.1% prevalence. ^[11,12] Mozambique had an estimated typhoid fever incidence of 107/100,000 population in 2019 and caused 590 fatalities. ^[13] This epidemiological surveillance report indicated that Nampula city in northern Mozambique had a typhoid fever positive rate of 38%, with adults over the age of 25 being the most affected. ^[14]

Life cycle

A capsule surrounds the entire bacterium and is responsible for its virulence and phagocytic invasion of the host. This pathogen weakens the intestinal epithelium by exploiting tight junction components to invade intestinal cells or tissue or to promote signaling responses that enhance its invasion. The pathogen tends to attack the intestinal mucosal lining through the action of microfolded cells (M cells), thus helping build up an undetectable bacterial load without clinical signs and symptoms, resulting in general bacteremia. This pathogen's important feature is triggering inflammation in the host when it invades. ^[15]

The ability to penetrate the intestinal mucosa correlates with the ability to invade non-phagocytic cells using the expression of a type III secretion system (T₃SS), which induces an increase in osmolarity and iron concentration, neutral pH, and a decrease in oxygen levels and allows injection of effector proteins directly into host cells, promoting actin polymerization and membrane rearrangements leading to *S. typhi* internalization. ^[15,16]

There are two main transmission cycles, the short transmission cycle and the long transmission cycle. The short transmission cycle refers to the contamination of food and water sources through feces in the immediate or close environment, subsequently facilitating transmission through poor or inadequate sanitation and hygiene standards. The long transmission cycle occurs in a wider environment when water is polluted with raw untreated sewage, or when untreated human feces are used as raw fertilizer for crops. ^[15,16]

Bacterial ingestion and systemic invasion are followed by a brief period of asymptomatic primary bacteremia, with an incubation period of from 7 to 14 days, but can range between 3 and 30 days, depending on the inoculum dose.^[16]

Pathogenesis

The typhoid fever is contracted mainly by bacteria present in water and food, which are contaminated by human or animal feces.^[1,7,17] After ingestion, the *Salmonella enterica* serotype *Typhi* penetrates the mucosa of the small intestine and invades the mononuclear phagocytes of the ileal Peyer's patches and mesenteric lymph nodes. Another key virulence factor expressed by most *S. typhi* strains is a polysaccharide capsule called the Vi (virulence) antigen. The Vi-capsule is encoded by the locus, which comprises several genes required for capsule biosynthesis and export. In the absence of the Vi-capsule, *S. typhi* is more sensitive to host immune activities.^[16-18]

The Vi-capsule has immunomodulatory features that contribute to disease development, such as restricting complement deposition, minimizing immunological activity, facilitating phagocytosis evasion, and inhibiting serum bacterial activity.^[16]

After an incubation period of 7 to 21 days, hematogenous dissemination occurs to the reticulo-endothelial system (liver, spleen and bone marrow), where *Salmonella* penetrate the histiocyte cells.^[17]

Early signs of bacteremia include fever and chills. Colonization of the gallbladder contributes to salmonella's elimination from the third week of illness. There is an inflammatory response at all sites of bacterial proliferation within the macrophages. Fever and other systemic symptoms appear to be caused by the release of endogenous pyrogens like interleukin I by infected macrophages, which contradicts the previously held belief that typhoid fever pathogenesis was mostly due to bacterial endotoxin. Hyperplasia of Peyer's patches, with involvement of the underlying mucosa (ulcerations), is responsible for intestinal manifestations such as abdominal pain, diarrhea, bleeding or intestinal perforation.^[17,19]

Clinical manifestations

Typhoid fever largely remains asymptomatic for 7 to 14 days, during which time fever is the predominant symptom. The patient's temperature may subsequently exceed 40°C in the following week, and skin eruptions may occur. Alterations in state of

consciousness, psychotic illnesses, psychomotor agitation, apathy, or torpor may be present at this time. The rashes may consist of pink patches, which is most frequent on the neck and abdomen but does not affect all patients. Other symptoms may include malaise, headache, distension, and abdominal pain, ^[7,17] table 1.

High temperature, relative bradycardia, hepatosplenomegaly, abdominal discomfort, and meningism are all physical examination findings. Major complications may include intestinal hemorrhage, intestinal perforation, urinary retention, pneumonia, thrombophlebitis, myocarditis, cholecystitis, nephritis, osteomyelitis, meningitis, anemia and delirium, with the latter two being the most prevalent. Relapses may occur in 3% to 20% of cases, 15 days after the temperature has normalized. ^[17,19]

The aforementioned periods are currently considered artificial because patients present various forms of the illness and clear boundaries between these periods aren't well-defined in practice. Also, there is the early or even indiscriminate use of antimicrobials. ^[17,19]

Table 1: Summary of the clinical manifestations of Typhoid Fever

Period	Time	Clinical findings	Reference
1. Invasive or initial period	After an incubation period of 7 to 21 days,	Fever, chills, headache, asthenia and dry cough, and prostration.	17,19
	Second week of illness	High fever, intense asthenia, torpor, hepatosplenomegaly, abdominal pain, diarrhea abdominal pain, diarrhea, macules or opular- erythematous lesions or rash on shoulders, chest and abdomen (<i>Roseoles typhi</i>).	
2. Period of decline	During and after the Fourth week of illness	Gradual improvement of symptoms and disappearance of fever.	17,19
3. Period of convalescence	After gradual improvement of general symptoms and disappearance of fever	Weight loss, weakness, loss of dynamism, skin peeling, and hair loss may occur.	17,19

Diagnosis

For typhoid fever, two types of diagnosis are used, namely differential and laboratory. In some cases, clinical-epidemiological diagnosis is also used.

Differential diagnosis

Typhoid has non-specific manifestations that overlap with those of other diseases like malaria, amoebiasis, leptospirosis, dengue, yellow fever, leishmaniasis, filariasis, viral hemorrhagic fever, tuberculosis, brucellosis, encephalitis, endocarditis, influenza and

infectious mononucleosis. Thus, differential diagnosis of individuals with typhoid fever is crucial. Additionally, attention should also be paid to other infections such as acute gastroenteritis, viral infections, infection with intracellular microorganisms and Other bacterial infections, which, because they present febrile conditions, can be confused with those caused by *Salmonella*.^[17,19]

In some African regions, malaria has been one of the biggest confounders of typhoid fever, as it is an endemic and highly prevalent disease in the country. Further complicating appropriate disease treatment and management are the numerous instances of patients self-medicating with antimalarials, due to difficulties in the diagnosis of typhoid fever in public health facilities.

Laboratory diagnosis

The laboratory diagnosis of typhoid fever is based, primarily, on the isolation and identification of the etiological agent, in the different clinical phases, from blood (hemoculture), feces (coproculture), bone marrow aspirates (myeloculture), urine (uroculture) and biopsy of typhic roseolas.^[1,17,20-23] However, Molecular diagnosis has also been used, mostly limited to research.^[22,23]

Treatment

Antibiotic intervention is the mainstay treatment of typhoid. The therapeutic regimen used in treating or managing depends mainly on the severity of the fever.^[24] The main antibiotics used are Ciprofloxacin, 500 mg twice daily orally or 400 mg twice daily intravenously for 5 to 7 days (10 to 14 days for severe typhoid),^[25] or Azithromycin, 500 mg once daily orally for 7 days (only for uncomplicated disease, and not recommended for severe disease).^[26]

Other treatments used include Ceftriaxone, 2 g once daily intravenously for 10-14 days for severe typhoid fever.^[26] Dexamethasone 3 mg/kg over 30 minutes intravenously, then 1 mg/kg every 6 hours for eight doses reduces mortality in patients with severe typhoid fever (e.g. those with delirium, coma, and shock). Importantly, resistance to Ampicillin, Chloramphenicol and Trimethoprim-sulfamethoxazole has spread globally.^[24] Without effective treatment, typhoid fever has a fatality rate of 10-30%, this figure can reduce to 1-4% in those receiving appropriate therapy.^[4]

Considerations for pharmacological options

Antibiotic therapy decreases the risk of death and shortens the clinical course of enteric fever. Fluoroquinolones (such as ciprofloxacin) are frequently used to treat adults with enteric fever and are regarded the preferred treatment for fluoroquino-lone-susceptible illnesses. Most infections in the United States, however, are acquired during international travel, particularly to locations where enteric fever is endemic and fluoroquinolone resistance among *Typhi* and *Paratyphi A* isolates is common. Fluoro-quinolone-resistant infections are also frequently resistant to nalidixic acid, a synthetic quinolone, and have been linked to treatment failure or delayed clinical response. [19,25]

In the United States, $\geq 90\%$ of *Typhi* and *Paratyphi a* infections in travelers to South Asia were either fluoroquinolone- or nalidixic acid-resistant, suggesting that treatment failures may occur among patients empirically treated with fluoroquinolones. Increasingly, azithromycin and ceftriaxone are being used to treat enteric fever. As of 2015, there was only 1 azithromycin-resistant *Typhi* isolate and no ceftriaxone-resistant *Typhi* or *Paratyphi A* isolates among the isolates tested by the CDC's National Antimicrobial Resistance Monitoring System. However, emerging resistance to azithromycin and ceftriaxone among *Typhi* strains has been reported outside the United States. [25]

Patients taking antibiotics may have a fever for 3 to 5 days, though the highest temperature normally drops each day. During the several days it takes for the fever to subside, patients may actually feel worse. If fever in a person with culture-confirmed typhoid or paratyphoid infection does not abate within 5 days, alternative antibiotics or persistent foci of infection, such as an abscess, bone or joint infection, and other extra-intestinal site of infection, should be considered. [25]

Relapses, reinfections and chronic carriage can also occur. In up to 10% of patients, relapse occurs 1 to 3 weeks after clinical recovery, requiring additional antibiotic treatment. An estimated 1- 4% of treated patients become asymptomatic chronic carriers, excreting bacteria in their stool for ≥ 12 months after acute infection and require prolonged treatment eradication. [18,20,25]

Treatment of uncomplicated cases

In situations of uncomplicated typhoid fever, WHO recommends fluoroquino-lone-based treatment such as floxacilin or ciprofloxacin. [6] Unless the patient is clinically unstable,

empiric antibiotic treatment should be avoided. If this is the case, treatment options should be addressed. The treatment for confirmed enteric fever with antibiotics is as follows: oral azithromycin 1 g on the first day, followed by 500 mg daily as first line, and meropenem IV 1 g every 8 hours as second line if patient cannot receive oral treatment.^[17]

Treatment of severe cases

For multidrug resistance (MDR) azithromycin or cefixime is used, while ceftriaxone or cefixime is recommended in case of quinolone resistance. Still, steroids can be used. In cases of septic shock, encephalitis, or coma, corticosteroids can be used as an adjuvant treatment.^[6,17]

Drug safety

There are some patient safety concerns with the current therapies, such as high potential of damage to growing joints and cartilage among children. Fluoroquinolones are relatively contraindicated for children in most countries, with the exception of multi-drug resistant infections where there is no suitable alternative. Fluoroquinolones can cause tendon injury in patients over 60 years of age, dysglycemia in the elderly, and diabetics.^[27]

Resistance to treatment

Isolates resistant to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole (Co-trimoxazole) were classified as multidrug resistant (MDR), while those that were MDR and resistant to fluoroquinolone and a third-generation cephalosporin were termed extensively drug resistant (XDR) (Table 2). Among 198 articles eligible for review, a total of 55,459 *S. typhi* isolates were tested for AMR (median 80; range 2-5,191 per study). Of the 2015-2018 isolates in Asia, 32.6% (1638 of 5032) were multidrug-resistant, 5.7% (167 of 2914) were resistant to third-generation cephalosporins, and 8.3% (148 of 1777) were resistant to azithromycin.^[26]

Two studies from Pakistan found that 2.6% of 546 isolates were extensively drug-resistant (XDR) *S. typhi*. In Africa, the proportion of MDR *S. typhi* isolates increased over consecutive decades from 1990 to 2018. Asia experienced expanding resistance with *S. typhi* developing resistance to multiple antimicrobial classes, including the emergence of XDR strains, posing a major threat. Meanwhile, Africa saw the expansion of MDR strains. Continued and heightened surveillance is crucial for informed empirical treatment

decisions. Incorporating antimicrobial resistance data is important for decisions regarding the introduction of typhoid conjugate vaccine (TCV).^[26] Over the past 40 years, *S. typhi* resistance has successively emerged against all primary antimicrobials, with multidrug resistance (MDR) emerging first in the 1990s, followed by reduced susceptibility to fluoroquinolones. Presently, South Asia faces high-level fluoroquinolone resistance, which poses a global dissemination risk.^[26]

Third-generation cephalosporins and azithromycin are becoming increasingly essential, yet resistance to these drugs is growing. Although clinical data on carbapenems and tigecycline are limited, reversal of sensitivity to chloramphenicol and cotrimoxazole is occurring in some circumstances. As a result, initial medications may still be useful in treating *S. typhi* infections.^[26] Table 3 outlines the novel investigational drugs

Table 2. Summary of studies on typhoid fever treatment resistance

Location	Treatment	Resistance mechanism	References
Ásia	Chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole	Chromosomal mutation in genes coding for DNA gyrase	26,28
África	Chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole	Chromosomal mutation in genes coding for DNA gyrase	
Germany	Cephalosporin	Production of beta lactamases	26,28
India	Ciprofloxacin	Mutations in regions with gyrA and gyrB, parC and parE genes	26,28

Abbreviations: DNA gyrase –gene that encodes the topoisomerase; gyrA and gyrB – are subunits of gyrase; ParC – Resolvase; parB – Nuclease.

Table 3. Ant-typhoid fever candidate under study

Name	Chemical class	Source	Type of test + IC ₅₀	References
Meropenem	carbapenems	Synthetic	UN	26
Tigecycline	tetracyclines	Synthetic	UN	
Phenalenone	Hydrocarbons	Synthetic	<i>In vitro</i> *	29
Furanone	Hydrocarbons	Synthetic	<i>In vitro</i> *	
Pectin Extracts and Hydrolysates	carbohydrates	Plant bark	<i>In vitro</i> (5.68µg), <i>In vivo</i> (44.45µg)	30
Lactobacillus	NA	Milk	<i>In vitro</i>	31

Abbreviations: NA – Not applicable; UN – uniformed. *IC₅₀ uniformed.

Coinfection of typhoid fever with other diseases

It was reported that typhoid fever can be associated with other diseases, with several factors influencing the outcome of these patients, including age, co-morbidity, and the time

between the onset of symptoms and the time of hospitalization, and these patients have a 30% mortality rate. [32-34]

Coinfection of typhoid fever with Malaria, is one of the most prevalent co-infections of typhoid fever. When malaria and typhoid fever co-infect, the symptoms are difficult to distinguish and can exacerbate the patient's condition. Furthermore, co-infection with malaria can weaken the patient's immune system, making them more vulnerable to subsequent illnesses. [32,35]

Coinfection of typhoid fever with Dengue fever can occur and if not timely diagnosed and treated can be fatal. These two diseases present similar symptoms, thus making accurate clinical diagnosis and treatment difficult. However, this co-infection can have a low lethality rate of 5.55%. [36]

Coinfection of typhoid fever with cholera. When it occurs in co-infection, cholera can worsen the symptoms of typhoid fever and increase the risk of dehydration. [37]

Coinfection of typhoid fever with tuberculosis or with HIV. A typhoid fever - tuberculosis co-infection can overload of the patient's immune system, making them more susceptible to serious complications. [37,38] A typhoid fever - HIV co-infection, can lead to an increased risk of serious complications. [35]

Typhoid fever can also co-infect with other diseases spread by contaminated food or water, such as hepatitis A and paratyphoid fever increasing the health risk. [33]

Since typhoid fever symptoms can overlap with those of other infectious diseases, clinical diagnosis can be challenging. It is thus important that doctors are aware of the patient's symptoms and perform adequate and appropriate tests like blood tests, stool tests, imaging, and other tests specific to each infectious disease to confirm the diagnosis. [37,39]

Preventing typhoid fever

Access to clean water, adequate sanitation and hygiene are part of a range of actions that contribute to the reduction of infectious diseases worldwide. [40] Currently, governments and non-governmental organizations (NGOs) have made efforts to provide these elements, given their importance in preventing transmittable diseases such as typhoid. Despite these attempts, there remains considerable obstacles worldwide, as not everyone has access to conventional latrines and must travel long distances to access clean drinking water. [41]

Additionally, in developing countries, mainly in Africa, there are still practices that are harmful to health such as open defecation, due to the lack of access to latrines, particularly in the slum settings, and inadequate disposal of solid waste, situations that contribute to the deterioration of environmental sanitation.^[42] Exposure to these risk factors contributes to the spread of typhoid fever, which requires coordinated action on prevention by political and community leaders, NGOs, local authorities and communities.^[43]

Public policies that promote public health are necessary through programs that encourage changes in habits and customs that endanger the population's own health, along with water supply and improved sanitation.^[44-49]

Prevention of typhoid fever can be attained with efforts involving improved hygiene and sanitation, establishing of communal latrines, providing access to clean and safe water and food, pasteurization of dairy products, identification and treatment of chronic carriers, community education and vaccination against fever as a tool to prevent the disease in a short time horizon.^[45] It is not enough just to implement intervention programs, but to ensure that they are efficient and effective. Similarly, improved economic conditions, education and environmental health have been associated with reductions in the typhoid burden.^[2]

Vaccine Development and Chemoprophylaxis

The development of vaccines effective against typhoid fever and the incorporation of appropriate immunization strategies to alleviate the increasing burden of the disease has been a subject of debate by various health sectors.^[46] In controlling the spread of typhoid fever, it is important to identify areas at risk, and understand the epidemiology of the disease. This allows for efficient distribution of new conjugate vaccines and new treatments that primarily focus on endemic areas.^[47] Additionally, a widespread up-take of TCVs, with their improved immunogenicity and longer duration of protection, has potential to combat AMR in typhoid endemic areas.

Furthermore, as ongoing efforts in vaccine development provides for those ex-posed to be minimally protected, it is crucial that the vaccination programs also include communication strategies for community outreach and engagement to combat vaccine apathy.^[48] For successful vaccine introduction in combating typhoid fever, appropriate strategies in advocacy and communications planning are key to ensure societal acceptance particularly in the vulnerable populations.

For a long time, two types of vaccines have been used to prevent typhoid: an injectable vaccine based on purified antigen (for recipients >2 years of age), and an oral live attenuated vaccine in capsule formulation, (for recipients >2 years of age).^[41] Two major disadvantages of these vaccines are that they did not provide long-lasting immunity and were not applicable for infants under 2 years of age.^[6]

Several types of vaccine are currently available for the prevention of typhoid fever such as Vivotif (Emergent Biosolutions), an enteric-coated capsule formation of the live attenuated Tyzta vaccine, and TYPHIM Vi (Sanofi Pasteur), a liquid form of the unconjugated polysaccharide Vi vaccine (ViPS), other vaccines available include the combined typhoid and hepatitis A vaccine VIVAXIM (Sanofi Pasteur). There are also two more recent generation tetanus toxoid-ViPS conjugate vaccines (typhoid conjugate vaccine) currently licensed.^[1]

Community strategies

Community-based typhoid control strategies are those that involve the active participation of communities affected by the disease in preventing and controlling its spread.^[50]

One of the key community-based typhoid control strategies is the promotion of personal and environmental hygiene. This includes teaching people how to wash their hands properly with soap and running water, how to store food properly to avoid contamination, and how to keep sanitation facilities clean and in good working order.^[6] At the same time discourage and promote alternatives to the consumption of raw or undercooked foods.

Another important strategy is promoting access to safe drinking water, since the lack of access to safe drinking water is a major contributor to the spread of typhoid fever.^[51] Communities can work together to ensure access to clean, safe drinking water, either by digging and insulating wells, installing water treatment systems or purifying water with chemicals, also to identify and control sources of contamination within their locality.^[51] Controlling the sources of contamination can be by regular cleaning of sewage channels, building proper sanitation facilities, proper collection and disposal of solid waste in specific areas.

Health education is another important strategy. Communities can be taught about causes of typhoid fever, how the bacterium is transmitted, and measures that can be taken

to prevent infection. Awareness campaigns can include lectures, distribution of educational leaflets and trainings for health workers, community leaders and trusted community custodians of frequently affected communities. [37,48]

Large-scale vaccination within the affected and vulnerable communities is also an important typhoid control strategy. Communities can work together with local health services to promote vaccination of individuals at risk of infection or spreading, such as children and food-handlers. [37,48,52]

Finally, it is important that communities have access to adequate health services for the diagnosis and treatment of typhoid fever. Health services should be accessible and available to all people, regardless of their socio-economic status. [53] This may be established through lobbying the local and central governments to construct fully functional, staffed and equipped health facilities.

From control to elimination

The challenge of controlling typhoid fever is often compounded by the lack of government support for adequate national surveillance in developing countries. Information from such surveillance provides information on the burden of disease in developing countries and assists in the development of strategies to improve health services, such as mass immunization in the most critical areas and the most susceptible groups.

For the control of typhoid fever in developing countries where this disease is ominous, WHO recommends the development and validation of improved diagnostic tests, sentinel surveillance sites to monitor vaccine impact and *S. typhi* trends, health facility-based surveillance with laboratory confirmation either through passive or active reporting for assessment of local disease trends and vaccine impact. [6]

Success in eliminating and reducing the spread of typhoid fever requires the integration of measures such as improvements in water quality, sanitation, and living conditions, together with the introduction of vaccines in more incident areas, and sensitizing people to implement such measures, as well as understanding how to change the risk factors present in the community. [54,55]

This approach was reinforced in a recent study, which showed that the use of TCVs together with implementing achievable household and culturally acceptable improvements like water quality, sanitation, and hygiene were directly correlated with a 70% reduction in the burden of infection in Dhaka, Bangladesh. [56]

Endemic countries should include TCVs as a priority in their Expanded Programme on Immunization (EPI) in which through routine childhood immunization campaigns, the children would benefit from this life-saving vaccine.^[3] At the same time, incorporating the TCV in the EPI plan would minimize the costs of administering the TCV among the children. The TCV is expected to attain the distribution objective in endemic areas between 2023 and 2026, but it is uncertain what quantity of doses will be required for this to occur. [57]

Conclusions and future perspectives

Typhoid fever remains a global health issue, particularly in locations where sanitary conditions are deteriorated. To effectively combat typhoid fever, a coordinated effort at the local, regional, and national levels is required, with investments in sanitation, health education, and disease control. Finally, more integrated studies considering socio-economic, environmental and other relevant factors should be carried out as they would greatly benefit governments and public health community understanding of the dynamics, transmission, impact and control of typhoid risk in development countries.

Summary of work done by the contributors:

ZMS, PAN, ASB and AAS contributed to the Concepts, Design, Definition of intellectual content AND manuscript review of this article. In the literature search, data acquisition and preparation of the manuscript, we had the contribution of ZMS, LEM, ASB, RVR, AREMG, JVM, BKFS, LRMBS, VIM, EBM, EFS and KHN.

Conflicts of interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. MASUET-AUMATELL, C.; Atouguia, J. Typhoid fever infection - Antibiotic resistance and vaccination strategies: A narrative review. *Travel Med Infect Dis.* 2021, 40, 1-15. <https://doi.org/10.1016/j.tmaid.2020.101946>
2. BHUTTA, Z.A.; Gaffey, M.F.; Crump, J.A., Steele, D.; Breiman, R.F.; Mintz, E.D.; et al. Typhoid fever: Way forward. *Am J Trop Med Hyg.* 2018, 99, 89-96. <https://doi.org/10.4269/ajtmh.18-0111>
3. BIRKHOLOLD, M.; Mwisongo, A.; Pollard, A.J.; Neuzil, K.M. Typhoid Conjugate Vaccines: Advancing the Research and Public Health Agendas. *J Infect Dis.* 2021, 224, 781-787. <https://doi.org/10.1093/infdis/jiab449>.

4. BUCKLE, G.C.; Walker, C.L.; Black, R.E. Typhoid Fever and Paratyphoid Fever: Systematic Review To Estimate Global Morbidity and mortality for 2010. *Journal of Global Health*. 2010, 2, e01401. <https://doi.org/10.7189/jogh.02020401>
5. STOESEER, N.; Eyre, D.; Basnyat, B.; Parry, C. Treatment of enteric fever (typhoid and paratyphoid fever) with third and fourth generation cephalosporins. *Cochrane Database of Systematic Reviews*. 2022, 11, e010452. <https://doi.org/10.1002/14651858.CD010452>
6. WHO. Would Health Organization. Vaccines and Biologicals: The diagnosis prevention and treatment of typhoid fever. Available online: <https://www.who.int/news-room/factsheets/detail/typhoid#:~:text=Persons%20with%20typhoid%20fever%20carry,serious%20complications%20or%20even%20death> (Accessed on 05 May 2023).
7. CRUMP, J.A. Progress In Typhoid Fever Epidemiology. *Clinical Infectious Diseases*. 2019, 68, 4-9. <https://doi.org/10.1093/cid/ciy846>
8. HANCUH, M.; Walldorf, J.; Minta, A.A.; Tevi-Benissan, C.; Christian, K.A.; Nedelac, Y.; et al. Typhoid Fever Surveillance Incidence, and Progress Toward Typhoid Conjugate Vaccine Introduction - Worldwide (2018-2022). *MMWR Morb Mortal Wkly*. 2023, 72, 171-176. <https://doi.org/10.15585/mmwr.mm7207a2>
9. FORSTER, D.P.; Leder, K. Typhoid Fever In Travellers: Estimating the Risk of acquisition by Country. *J Travel Med*. 2021, 28, e150. <https://doi.org/10.1093/jtm/taabi50>
10. CRUMP, J.A.; Luby, S.P.; Mintz, E.D. The Global Burden Of Typhoid Fever. *Bulletin of The World Health Organization*. 2004, 82, 346-353.
11. SEJVAR J.; Lutterloh, E.; Naiene, J.; Likaka, A.; Manda, R.; Nygren, B.; et al. Neurologic manifestations associated with an outbreak of typhoid fever, Malawi--Mozambique, 2009: an epidemiologic investigation. *PLoS One*. 2012, 7, e46099. <https://doi.org/10.1371/journal.pone.0046099>.
12. LOVANE, L.; Martinez, M.J.; Massora, S.; Mandomando, I.; Ussene, E.; Jordao, D.; et al. Carriage prevalence of *Salmonella enterica* serotype Typhi in gallbladders of adult autopsy cases from Mozambique. *J Infect Dev Ctries*. 2016, 10, 410-2. <https://doi.org/10.3855/jidc.7306>. PMID: 27131005.
13. BARDEN of Typhoid in Mozambique. Available online: https://www.coalitionagainststtyphoid.org/wp-content/uploads/2022/12/TakeonTyphoid_Mozambique_Infographic_Nov2022.pdf (Accessed on 12 November 2023).
14. DIREÇÃO Provincial de Saúde. Informe de Vigilância Epidemiológica de febre Tifoide. *DPS-NPL-Moçambique*. 2023, 1, 1-2.
15. KHAN, M.; Shamim, S. Understanding the Mechanism of antimicrobial Resistance and Pathogenesis of *Sarmonella enterica* Serovar Typhi. *Microorganisms*. 2022, 10, e2006. <https://doi.org/10.3390/microorganisms10102006>
16. GIBANI, M.M.; Brito, C.; Pollard, A.J. Typhoid and Paratyphoid Fever: A call to Action. *Curr Opin Infect Diseases*. 2018, 31, 440-448. <https://doi.org/10.1097/QCO.000000000000479>
17. PINTANEL, S.R.; Cecconello, S.T.; Centeno, L.N. Análise da Correlacao entre os Indicadores de Saneamento Basico e as doencas de Veiculacao Hidrica em Municipios do Sul do Rio Grande do Sul. *Ambientale*. 2021, 13, 41-52.
18. SANTANA, L.A.; Pereira, S.D.; Antonio, V.E.; Castro, A.S.; Miguel, P.S.; Moreira, T.R. Febre Tifoide: Revisão para a Pratica Clinica. *Revista Cientifica Fagoc Saude*. 2021, 6, 73-83.
19. MS. Ministerio da Saúde. Manual Integrado de Vigilancia e Controle da Febre Tifoide. Available online: <https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/f/febre-tifoide/publicacoes/manual-integrado-de-vigilancia-e-controle-da-febre-tifoide/view> (Accessed on 07 December 2023).
20. WASIHUN, A.G.; Wlekidan, L.N.; Gebremariam, S.A.; Muthupandian, S.; Welderufael, A.L.; Haile, T.D.; et al. Diagnosis and Treatment of Typhoid Fever and Associated Prevailing Drug Resistance in Northern Ethiopia. *Internacional Journal of Infectious Diseases*. 2015, 35, 96-102. <https://doi.org/10.1016/j.ijid.2015.04.014>

21. WIJEDORU, L.; Mallett, S.; Parry, C.M. Rapid Diagnosis Tests for Typhoid and Paratyphoid (Enteric) Fever. *Cochrane Database Syst Rev.* 2017, 5, e008892. <https://doi.org/10.1002/14651858.CD008892>
22. FREMPONG, S.N.; King, N.; Sagoo, G.S. The Cost-effectiveness of Using Rapid Diagnosis Testes for the Diagnosis of Typhoid Fever in patients with Suspected Typhoid Fever. *Expert Review of Pharmacoeconomics e Autcomes Reseach.* 2022, 22, 391-397. <https://doi.org/10.1080/14737167.2022.2012453>
23. DAS, S.; Ray, U.; Akhter, I.; Chattopadhyay, A.; Paul, D.K.; Dutta, S. Evaluation of fliC-d based direct blood PCR assays For Typhoid Diagnosis. *BMC Microbiology.* 2016, 16, e108. <https://doi.org/10.1186/s12866-016-0723-6>
24. PAPANAKIS, M.A.; McPhee, S.J. Quick Medical Diagnosis & Treatment 2021-Enteric fever (typhoid fever) 2021. Available online: <https://accessmedicine.mhmedical.com/content.aspx?bookid=2986§ionid=251092305> (Accessed on 25 June 2023).
25. GRACE, D.A.; Michael, J.H. Typhoid & Paratyphoid Fever. Centers for Disease Controls and Prevention. Available online: <https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/typhoid-and-paratyphoid-fever> (Accessed on 20 February 2023).
26. KARKEY, A.; Thwaites, G.E.; Baker, S. The evolution of Antimicrobial Resistance in Sarmonella Typhi. *Curret Opinion in Gastroenterology.* 2018, 34, 25-30.
27. CRUMP, J.A.; Karlason, M.S.; Gordon, M.A.; Parry, C.M. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance of Invasive *Sarmonella* Infections. *Clinical Microbiology Reviews.* 2015, 28, 901-937. <https://doi.org/10.1128/CMR.00002-15>
28. FRANCISCO, M. Caracterização microbiológica e molecular das estirpes de *Salmonella spp* isoladas em amostras de fezes, águas residuais e em ovos de produção aviárias na região de Luanda e dos seus perfis de resistência aos antimicrobianos – o seu impacto na saúde pública. Available online: <https://run.unl.pt/handle/10362/59484> (Accessed on 18 January 2023).
29. MUJAWAR, S.; Gatherer, D.; Lahiri, C. Paradigm shift in Drug Repurposing From Phenalenone to Phenaleno-Furanone to combat Multi-Drug Resistant *Salmonella enterica* Serovar *Typhi*. *Frontiers in Celular and Infection Microbiology.* 2018, 8, e402. <https://doi.org/doi:10.3389/fcimb.2018.00402>
30. ZOFOU, D.; Shu, G.L.; Tendo, J.F.; Tabouguia, M.O.; Assob, J.C. *In Vitro* and *In Vivo* Anti-Sarmonella Evaluation of Extracts and Hydrolysates from " Cas Mango" (*Spondias dulcis*). *Evid Based Complement Alternat Med.* <https://doi.org/10.1155/3578402>
31. DAIM, A.A.; Hassouna, N.; Hafez, M.; Ashor, M.S.; Aboulwafa, M.M. Antagonistic Activity Of *Lactobacillus* Isolates Against *Sarmonella typhi* *In Vitro*. *BioMed Reseach International.* 2013, 2013, e680605. <https://doi.org/10.1155/2013/680605>
32. RYANB, J.R.; Jason, E.T. Diagnostics for invasive *Salmonella* infections: current challenges and future directions Jason. *Physiol Behav.* 2016, 176, 139-48. <https://doi.org/10.1016/j.vaccine.2015.02.030>
33. MELTEZER, E.; Stienlauf, S.; Leshem, E.; Sidi, Y.; Schwartz, E. A large outbreak of *Salmonella paratyphi* a infection among israeli travelers to Nepal. *Clin Infect Dis.* 2014, 58, 64-359. <https://doi.org/10.1093/cid/cit723>
34. DUDAKA, A.; Sundaramurthi, S.; Vijayakumar, C.; Elamurugan, T.P.; Jagdish, S. Coinfection Fever With Tuberculosis: A Challege to Surgical Management. *Cureus.* 2020, 12, e8540. <https://doi.org/10.7759/cureus.8540>
35. Mogasale, V.; Maskery, B.; Ochiai, R.; L.; Lee, J. S.; Mogasale, V.V.; Ramani, E. Burden of typhoid fever in low-income and middle-income countries: A systematic, literature-based update with risk-factor adjustment. *Lancet Glob Heal.* 2014, 58, 570-80. [http://dx.doi.org/10.1016/S2214-109X\(14\)70301-8](http://dx.doi.org/10.1016/S2214-109X(14)70301-8)
36. MAHATO, A.K.; Shrestha, N.; Ghati, S.B.; Shah, M. Typhoid Fever Among Patients Diagnosed With Dengue in a Tertiary Care Centre: A Descriptive Cross Sectional Stdy. *Journal of Nepal Medical Associaction.* 2022, 60, 714-717. <https://doi.org/10.31729/jnma.7624>
37. SABIN, A.B. Control of infectious diseases. *J Infect Dis.* 1970, 21, 91-4. <https://doi.org/10.1093/infdis/121.1.91>

38. McLennan, H. Acetylcholine metabolism of normal and axotomized ganglia. *The Journal of Physiology*. 1954, 124, 113–116. <https://doi.org/10.113/jphysiol.1954.sp005090>
39. OCHIAI, R.L.; Acosta, C.J.; Danovaro-Holliday, M.C.; Baiqing, D.; Bhattacharya, S.K.; Agtini, M.D.; et al. A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bull World Health Organ*. 2008, 86, 260–8. <https://doi.org/10.2471/blt.06.039818>.
40. ROSS, A.G.; Rahman, M.; Alam, M.; Zaman, K.; Qadri, F. Can we ‘WaSH’ infectious diseases out of slums? *Int J Infect Dis*. 2020, 92, 130–2. <https://doi.org/10.1016/j.ijid.2020.01.014>
41. CHARD, A.N.; Trinies, V.; Moss, D.M.; Chang, H.H.; Doumbia, S.; Lammie, P.J. The impact of school water, sanitation, and hygiene improvements on infectious disease using serum antibody detection. *PLoS Negl Trop Dis*. 2018, 12,1–16. <https://doi.org/10.1371/journal.pntd.0006418>
42. HUTTON, G. Global costs and benefits of reaching universal coverage of sanitation and drinking-water supply. *J Water Health*. 2013, 11:1–12. <https://doi.org/10.2166/wh.2012.105>
43. KHANAN, F.; Ross, A.G.; McMillan, N.A.; Qadri, F. Toward Typhoid Fever Elimination. *Int J Infect Dis*. 2022, 119, 41–3. <https://doi.org/10.1016/j.ijid.2022.03.036>
44. STEELE, A.D.; Hay Burgess, D.C.; Diaz, Z.; Carey, M.E.; Zaidi, A.M. Challenges and Opportunities for Typhoid Fever Control: A Call for Coordinated Action. *Clin Infect Dis*. 2016, 62, 4–8. <https://doi.org/10.1093/cid/civ976>
45. MARCHELLO, C.S.; Birkhold, M.; Crump, J. A. Complication and Mortality of Typhoid Fever: A Global Systemic Review and Meta-Analysis. *Journal of Infection*. 2020, 81, 902–910. <https://doi.org/10.1016/j.jinf.2020.10.030>
46. BHUTTA, Z.A.; Gaffey, M.F.; Crump, J.A., Steele, D.; Breiman, R.F.; Mintz, E.D.; et al. Typhoid fever: Way forward. *Am J Trop Med Hyg*. 2018, 99, 89–96. <https://doi.org/10.4269/ajtmh.18-0111>
47. WAIN, J.; Hendriksen, R.S.; Mikoleit, M.L.; Keddy, K.H.; Ochiai, R.L. Typhoid fever. *Lancet*. 2015, 85, 1136–45. [https://doi.org/10.1016/S0140-6736\(13\)62708-7](https://doi.org/10.1016/S0140-6736(13)62708-7)
48. JOHN, J.; Van Aart, C.; Grassly, N.C. The Burden of Typhoid and Paratyphoid in India: Systematic Review and Meta-analysis. *PLoS Negl Trop Dis*. 2016, 10, 1–14. <https://doi.org/10.1371/journal.pntd.0004616>
49. SUR, D., Von Seidlein, L.; Manna, B. Community-based assessment of safety and efficacy of two-dose Vi typhoid fever vaccine in tea garden communities in India. Available online: https://main.icmr.nic.in/sites/default/files/annual_repoorts/Annual-Report_2005-2006_ICMR_Headquarters-Delhi-English.pdf (Accessed on 20 November 2023).
50. HOSOGLU S, Celen MK, Geyik MF, Akalin S, Ayaz C, Acemoglu H, et al. Risk factors for typhoid fever among adult patients in Diyarbakir, Turkey. *Epidemiology and Infection*. 2006, 134, 612–6. <https://doi.org/10.1017/S0950268805005583>
51. FAROOQUI, A.; Khan, A.; Kazmi, S.U. Investigation of a community outbreak of typhoid fever associated with drinking water. *BMC Public Health*. 2009, 1, 1–6. <https://doi.org/10.1186/1471-2458-9-476>
52. CUTTS, F.T.; Izurieta, H.S.; Rhoda, D.A. Measuring Coverage in MNCH: Design, Implementation, and Interpretation Challenges Associated with Tracking Vaccination Coverage Using Household Surveys. *PLoS Med*. 2013, 10, e1001404. <https://doi.org/10.1371/journal.pmed.1001404>
53. UNICEF. Strategy for Health 2016-2030. Available online: <https://www.unicef.org/media/119736/file/UNICEF-Strategy-for-Health-2016-2030.pdf> (Accessed on 16 October 2023).
54. GESSNER, B.D.; Halloran, M.E.; Khan, I. The case for a typhoid vaccine probe study and overview of design elements. *Vaccine*. 2015, 33, 30–35. <https://doi.org/10.1016/j.vaccine.2015.03.085>
55. PITZER, V.E.; Bowles, C.C.; Baker, S.; Kang, G.; Balaji, G.; Farrar, J.J. Predicting the Impact of Vaccination on the Transmission Dynamics of Typhoid in South Asia: A Mathematical Modeling Study. *PLoS Negl Trop Dis*. 2014, 8, e2642. <https://doi.org/10.1371/journal.pntd.0002>

56. TADESSE, B.T.; Khanam, F.; Ahmmed, F.; Im, J.; Islam, M.T.; Kim, D.R. Prevention of Typhoid by Vi Conjugate Vaccine and Achievable Improvements in Household Water, Sanitation, and Hygiene: Evidence From a Cluster-Randomized Trial in Dhaka, Bangladesh. *Clin Infect Dis*, 2022, 75, 1681–7. <https://doi.org/10.1093/cid/ciac289>
57. DEBELLUT, F.; Hendrix, N.; Pitzer, V.E.; Neuzil, K.M.; Constenla, D.; Bar-Zeev, N.; et al. Forecasting demand for the typhoid conjugate vaccine in low and middle-income countries. *Clin Infect Dis*. 2019, 68,154–160. <https://doi.org/10.1093/cid/ciy1076>