Study of Typhoid Epidemiology by Serological Test

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Abstract

Salmonella enterica subspecies enterica serovar Typhi, a Gram-negative bacterium, causes typhoid disease *(S.Typhi).* The public health problem of typhoid fever is serious. Typhoid fever is a serious public health hazard, causing an estimated 22 million infections and 200 000 deaths globally. The most typical route to get the disease is by ingestion of feces-contaminated food or drink, followed by urine or vomitus from patients or carriers. A prolonged low-grade fever, headache, dry cough, gastrointestinal disturbances, coated tongue, and rose spots are some of the most prevalent clinical signs. A simple, reliable test that may be done in small facilities is urgently required. For typhoid fever diagnosis, we looked at the results of the Widal test, blood culture, and Typhidot assays. *S. Typhi's* biology, virulence, serological test, and prevention are all discussed in this article.

Keywords: Typhoid fever, *Salmonella enterica serovar Typhi (S. Typhi)*, Serologic tests, Widal, blood culture, prevention.

Introduction

Systemic infection with *Salmonella enterica subspecies serovars Typhi* and *Para typhi* A, B, and C causes typhoid and paratyphoid fevers, which are together known as enteric fevers [1]. The germ that causes typhoid fever *Salmonella* is spread through drinking contaminated water or eating infected food. When bacteria enter the human body, it travels through the intestines and enters the bloodstream [2]. Abdominal discomfort, fever, stomach-ache, and either constipation or diarrhoea are all signs of this condition. As the condition progresses, a high temperature and severe diarrhoea develop. Typically, the incubation phase lasts ten to fourteen days [3][4]. In underdeveloped nations, it remains a severe health danger, and in Asia, it is the most prevalent cause of community-acquired bacteraemia. On a global scale, it is estimated that annually, there were about 21.5 million illnesses, resulting in More than 200 000 people died in the year 2000 [5][6]. *Salmonella enterica serovar Typhi (S. Typhi)* isolation in blood culture validates typhoid fever diagnosis and is commonly employed as a gold standard for the validation of novel diagnostic tests. However, it Sensitivity is low, ranging from 40% to 60% [7]. The Widal test, which evaluates agglutinating antibody titers against S. Typhi lipopolysaccharide (LPS) "O" and flagellar "H" antigen, is the most widely used serologic test. Only a 30% positive connection exists between test findings and culture-confirmed typhoid illness [8]. A number of new-generation serology-based rapid diagnostic tests for typhoid fever have been commercially available, including Typhidot (Malaysian Bio - Diagnostics Research SDN BHD, Malaysia), TUBEX (IDL Biotech, Sollentuna, Sweden), and Multi-Test Dip-S-Tics (PanBio IndxBaltimore, MD, USA), whose performance has been evaluated globally. However, none of these assays were time tested or showed long-term findings when evaluated in various endemic settings [9].

Pathogenesis

Unlike *S. typhimurium*, *S. typhi* uses a stealth method to colonise deeper tissues of the body by avoiding an early inflammatory reaction in the stomach of the human host [10][11]. The pathophysiology of typhoid fever that we provide is primarily based on a mouse model in which *S. typhimurium* induces a systemic infection that is comparable to typhoid. *S. typhi* most likely infects the terminal ileum's gut mucosa by specialized antigen-sampling cells called M-cells that overlie gut-associated tissue,[12] enterocytes, or a paracelluar pathway [13]. The bacteria cling to the intestinal mucosa in the terminal ileum via interacting with the cystic fibrosis transmembrane conductance regulator protein, an epithelial receptor [14]. The encouragement of intestinal epithelial cells to raise membrane receptor levels, resulting in increased bacterial ingestion and submucosal translocation, is a crucial early stage in the infectious process [15]. Infiltration of peripheral blood leucocytes into the lamina propria is caused by bacterial invasion. This invasion is mediated by epithelial cells secreting cytokines in response to bacterial lipopolysaccharide, a component of gram-negative bacteria's cell wall. Lipopolysaccharide stimulates transcription factors in lymphocytes by signalling through the Toll-like receptor 4 complex in mammals [16][17]. Invading bacteria are taken up by macrophages, which then die as a result of caspase-1-mediated apoptosis triggered by *salmonella* [18].

The bacteria reach the intestine's lymphoid tissue, where they are discharged into the mesenteric nodes, thoracic duct, and eventually the systemic circulation. Within 24 hours of ingestion, the organism reaches the spleen, liver, bone marrow, and other parts of the reticuloendothelial system, where it lives and multiplies in monocytic cells, causing primary bacteraemia [19]. Bacteria are shed back into the circulation, signalling the start of the clinical disease and the maintenance of a low level of bacteremia. A molecular mechanism for *salmonella* persistence in the host, as shown in the typhoid carrier state, has been postulated [10]. The allele of the Nramp1 gene expressed on macrophages has been related to differences in mice susceptibility to *S. typhimurium* [20]. During the early stages of infection, Nramp1 regulates the exponential development of salmonella in the reticuloendothelial system. Mice carrying the wildtype Nramp1 allele did not die after being

inoculated with *S. typhimurium* orally, but they did become evenly infected, just like chronic typhoid carriers [21]. Despite a strong antibody response, *Salmonella* remained in tiny quantities, mostly in the macrophages of the mesenteric lymph nodes or spleen (or both). Antibodies to neutralise interferon might be used to reactivate intracellular salmonella and transmit it throughout the body, showing that the host cytokine interferon is critical for salmonella replication and disease suppression.

Diagnosis method

Recent studies of typhoid fever diagnosis and treatment show that typhoid fever laboratory diagnosis is mostly reliant on the identification of organisms in blood by PCR or culture. In Africa and Asia, the Widal test for antibody production is inaccurate, and new-generation serology assays like typhidot and tubex have not shown to be trustworthy. The typhoid– paratyphoid diagnostic assay is a promising novel test format. which can detect IgA. This approach uses ELISA to identify circulating IgA for typhoid fever diagnosis and enhances sensitivity (to 100 percent) by amplifying the signal by isolating and incubating peripheral blood cells. Isolation of *S. typhi* or *S. paratyphi* from stool, bone marrow, blood, or duodenal fluid is required to confirm typhoid or paratyphoid fever. The researchers used skin cultures from rose patches, buffy coats, and blood clots that had been treated with streptokinase [22][23][24][25]. In 80– 95 percent of typhoid patients, bone marrow aspirate culture is positive.[22][23][24][26]. To equal the positive rate of 1 mL of bone marrow, more than 10 mL of blood must be cultured. Long-term sickness and antibiotic therapy benefit from bone marrow cultures. The most common method of diagnosis is blood culture. *Salmonella* is detected in 30–90% of individuals with clinical typhoid using conventional broth cultures [24][27][28]. Blood culture yield is determined by the amount of blood and the ratio of blood to broth: To maintain an ideal ratio of 1 to 12, 2–5 mL of blood is required. In youngsters with a higher bacterial content in their blood, 10-15 mL of blood is adequate [28][29]. The yield is harmed by improper laboratory procedures, antimicrobials, and failure to maintain ambient temperatures of 15–40C during specimen transit. Stool isolation of *S. typhi* is inadequate for diagnosis, while blood culture only improves diagnosis minimally. It is, nonetheless, necessary for carrier detection. Serological assays based on agglutination of Vi antigens have a sensitivity of 70–80% and a specificity of up to 95% in detecting *S. typhi* carriers [30].

Diagnosis has now become a standard clinical procedure all around the world. Since a result of the wide range of diseases that affect people, and as new diseases emerge on a daily basis, diagnosis is critical for treating those who are afflicted.

Table 1: Isolates in blood culture

Age group	Number of patients	Males	Females	*S. typhi* isolated	*S. paratyphi* A isolated
18-30	12	8	4	6	2
31-40	10	5	5	4	—
41-50	8	5	3	—	1

Fig 1: Blood culture bottle

The Widal test is one such way for diagnosing enteric fever by assuming the individual's symptoms. This test is no longer used in any other affluent nations, such as the United States, because enteric fever is considered an endemic disease with inadequate resources for quick testing alternatives. This procedure is simple to use, however there are issues regarding the test's reliability. This test is not only for typhoid fever; it may also be performed to confirm that the person has no other diseases.

The Widal test detects agglutinating antibodies to the O (somatic) and H (flagellar) S typhi antigens, which emerge one to ten days after the commencement of the illness. Because O and H antigens and cross-reacting epitopes with other Enterobacteriaceae are shared, the sensitivity, specificity, and predictive values given by various centres varies [31]. The Widal test's clinical use is limited by the large frequency of false-positive and false-negative findings. To make a diagnosis, data from a single acute sample should be compared to local cut-off values, or there should be a four-fold difference in antibody titres between convalescent and acute sera [32][33]. The sensitivity and specificity for identifying blood-culture-positive cases of typhoid fever were 89% and 53% for multi-test dip-sticks (PANBIO INDX, Baltimore, MD, USA), 79% and 89% for typhidot (Malaysian Biodiagnostic Research SDN BHD, Malaysia), and 78% and 89% for tubex test (IDL Bideh, Solletuna, Sweden) in a study, [34].

Fig 2: Widal plate

SAMPLE	CONTROL	IgM	IgG	RESULT
1	Present	Detect	Detect	Positive both IgM and IgG
2	Present	Detect	_____	Positive IgM
3	Present	_____	Detect	Positive IgG

4	_____	_____	_____	**Invalid**
5	**Present**	_____	_____	**Negative**

Table 2: Typhidot

Treatment

The most common treatments are fluoroquinolones, azithromycin, and third-generation cephalosporin medicines, with chloramphenicol being used in areas where sensitive strains are found. Most carriers who do not have gallstones can be treated with a long course of antimicrobials. After 28 days, 750 mg of ciprofloxacin twice daily cured roughly 80% of carriers, whereas 11 of 12 carriers treated with 400 mg norfloxacin twice daily had negative stool and bile cultures for S typhi [35][36]. Cholecystectomy and antimicrobial treatment may be necessary in people with gallstones. People recuperating from typhoid fever, as well as carriers, should be prohibited from any activity involving food preparation and serving.

Prevention

Safe food, safe water, personal cleanliness, and proper sanitation are the most important preventative interventions [37]. With the rise of antibiotic resistance, the necessity of prevention has risen dramatically. Safe drinking water and adequate sanitation, on the other hand, are costly and are frequently tied to economic development. Vaccination is another powerful strategy in the fight against typhoid disease. Typhoid vaccination is beneficial for travellers from industrialized nations visiting typhoid-endemic countries, for avoiding and controlling outbreaks, and for children aged 2–19 years in endemic areas [37]. In industrialised countries, travel to endemic disease zones is the major cause of typhoid fever. India, Pakistan, Mexico, Bangladesh, the Philippines, and Haiti accounted for 76% of travel related incidents [38]. Persons who stayed at their vacation destination for 4 weeks or less were responsible for 37% of these instances, while people who stayed for 2 weeks or less were responsible for 16% People visiting family and friends accounted for 80% of the incidents. Vaccination should be addressed for visitors to these countries, particularly those staying for two weeks or longer and visiting friends and family. Although the old parenteral whole-cell typhoid-paratyphoid A and B vaccine proved effective against both typhoid and paratyphoid fevers, it was generally phased out due to severe side effects [39]. Typhoid fever vaccines, one based on Vi polysaccharide and the other on whole cell live attenuated bacteria, are now available. Although it has yet to be tried in newborns, a newer Vi-conjugate vaccine is particularly effective in children under the age of five. For the time being, there is no licenced paratyphoid fever vaccine.

Vi polysaccharide vaccine

This vaccine is approved for use in people above the age of two and is administered as a single subcutaneous or intramuscular dose. For roughly 3 years following inoculation, the vaccine is moderately effective. Every three years, revaccination is advised. However, 10 years after immunisation, 58 percent of individuals in a field study in South Africa still exhibited protective antibody levels [43]. In a population inoculated before or during an outbreak in China, this vaccine showed roughly 70% protective effectiveness [40]. The Vi vaccine \scan be administered simultaneously with other vaccines relevant for foreign travellers such as yellow fever as well as hepatitis A [41][42][44].

Ty21a vaccine

This live oral vaccination is authorised for use in persons aged 6 and above and is available in enteric-coated or liquid formulations. Only a few nations presently sell the liquid formulation for younger children. 3 doses, two days apart, are advised.

Antimicrobials should be avoided for at least 7 days before to and after immunisation. For up to 3 years following immunisation, the vaccine is fairly effective. In endemic locations, a booster dosage is suggested every three years, and travellers should be revaccinated every year. During field testing in Chile, herd immunity was demonstrated. A booster dose is recommended every three years in endemic areas, and visitors should be revaccinated every year. Herd immunity was proven during field testing in Chile [45][46]. The vaccine can be given simultaneously with other vaccines and with antimalarial prophylaxis [47]. Both of these approved vaccinations have similar efficacy in underdeveloped countries. Ty21a has the benefit of being given orally, making it simpler to immunise large groups of youngsters, such as in schools. The Ty21a vaccine, particularly the enteric coated capsule version, is not approved for children aged 2 to 5. The Vi vaccine has the benefit of being able to be utilized for young preschool children in areas where typhoid fever is prevalent in this age range. The vaccination, on the other hand, is not approved for use in children under the age of two. Vaccine Adverse Effects Reporting System post-marketing surveillance for typhoid fever vaccinations from 1990 to 2002 revealed just a few reports of death, hospitalisation, permanent disability, or life-threatening illness. Dizziness and pruritis were common unexpected effects for the Vi vaccination, whereas weariness and myalgia were common with the Ty21a vaccine. Ty21a gastroenteritis and Vi vaccine-induced stomach discomfort have both been previously reported side effects.

VI- conjugate vaccine

The Vi-conjugate vaccine, administered to Vietnamese children aged 2–5, provided 91% protection against typhoid 27 months after immunisation, with geometric mean titres of 761 ELISA units for those inoculated at the age of 2–3 [48]. The effectiveness of this compound was maintained after 46 months of vaccination: protection was 89% (95% CI 76% –97%) across the whole duration [49]. The researchers advise that a protective level of antibody to immunoglobulin G be decreased from 7 to 352 ELISA units based on antibody titres after 46 months after immunisation. This vaccine might be used in children under the age of two, and it could be included in the Expanded Programme on Immunization immunisation regimens.

Conclusion

Typhoid fever is a serious public-health concern in Southeast Asia, the Middle East, Africa, and South America, affecting primarily children and young people. Treatment for typhoid fever is getting increasingly challenging as multidrug-resistant bacteria develop fluoroquinolone resistance. Although complete ciprofloxacin resistance in non-typhoid salmonella has arisen, no fully ciprofloxacin-resistant *S typhi* has been identified. In the face of rising antibiotic resistance, effective immunization and non-vaccine based preventative efforts are becoming increasingly vital. In an evaluation of three commercial kits, the sensitivity and specificity for identifying blood-culture-positive cases of typhoid fever was 89% and 53% for multi-test dip-sticks, 79% and 89% for typhidot, 78% and 89% for tubex test as compared with 64% and 76% for Widal. Humans are the only ones who can contract *S. typhi*. After being eliminated from local areas, the organism does not survive long in any environmental reservoir. Individual pseudogene mutations from *S. typhi* isolates were analysed, and it was discovered that the same mutations were found in various isolates. This clearly shows that the organism has only appeared once and is unlikely to develop from other *S typhi* serotypes. To prevent typhoid fever, greater sanitation, better diagnostics for early diagnosis and treatment of patients and carriers, and mass immunisation are all viable approaches. All of these criteria suggest that worldwide typhoid eradication is theoretically achievable and should be considered as a global health concern.

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Conflicts of interest

The authors declare no conflicts of interest.

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