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TYPHOID AND PARATYPHOID A AND B: THE RELEVANCE OF IMPROVING MEASURES FOR THEIR DETECTION AND TREATMENT

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Abstract. *Salmonella enterica serovars Typhi* and *Paratyphi (S. Typhi and S. Paratyphi)* are the cause of enteric fever, a potentially fatal systemic febrile illness. Regretfully, despite ongoing progress in the field, the disease's burden is still significant, mostly because of the worldwide proliferation of different drug-resistant strains of Salmonella. For the condition to be effectively controlled, a precise diagnosis is essential. Feverish bacterial diseases like typhoid and paratyphoid (enteric fever) are prevalent in many low- and middle-income nations. Due to widespread resistance to earlier, first-line antibiotics, the World Health Organization (WHO) currently advises therapy with azithromycin, ciprofloxacin, or ceftriaxone. Resistance patterns change over time and differ depending on the region. Ciprofloxacin is frequently ineffective in South Asia due to fluoroquinolone resistance. In Pakistan, enteric fever strains that are highly resistant to drugs have surfaced. Susceptibility to outdated first-line antibiotics, such chloramphenicol, has resurfaced in some parts of the world. The use of azithromycin and fluoroquinolones in the treatment of enteric fever has previously been the subject of a Cochrane Review; however, the use of cephalosporins has not been well examined, and the best course of action and length of treatment are unknown. The potentially serious and sometimes fatal bacteremic illnesses caused by *Salmonella enterica serotypes Typhi, Paratyphi A, Paratyphi B* (tartrate negative), and *Paratyphi C* are known as typhoid fever (for the Typhi serotype), paratyphoid fever (for the Paratyphi serotypes), and enteric fever. There are currently no diagnostic techniques for identifying asymptomatic carriers, and laboratory assays exhibit subpar sensitivity and specificity. To find more precise biomarkers for early detection and asymptomatic carrier detection, a number of research initiatives have used systemic techniques. The advantages and disadvantages of the enteric fever diagnostic tests that are now on the market, the progress of research toward better diagnostic tests, and the difficulties in finding new, optimal biomarkers and tests are all covered in this review.

Keywords. Antimicrobial resistance, enteric fever surveillance, typhoid fever diagnosis, *Salmonella, Salmonella Typhi,* chromosomal gene changes.

Introduction. The bacteria that cause enteric fever only comes from humans; no environmental or animal reservoirs have been found. Consumption of water or food tainted by the excrement of an acutely infected or convalescent individual, or a person with chronic, asymptomatic carrier, can result in typhoid and paratyphoid fever. In low- and middle-income nations with endemic diseases, limited access to healthy food and water, and inadequate sanitation, the risk of infection is considerable. Enteric fever outbreaks have been connected to large gatherings in endemic areas. One uncommon method of transmission is sexual contact, especially between guys who have intercourse with other men. In low- to middle-income nations in Asia, Africa, and South America, enteric fever—also known as typhoid fever and paratyphoid fever—is a prevalent bacterial illness with high rates of morbidity and mortality that is linked to inadequate sanitation and a lack of clean drinking water. According to estimates from the World Health Organization (WHO), there are up to 21 million cases of enteric fever and 161,000 fatalities annually [1-6]. However, because this estimate was derived from a small number of surveillance studies using current diagnostic methods, the true burden of the disease is unknown. Enteric fever is caused by human-restricted Salmonella enterica serovars *Typhi* and *Paratyphi A, B,* and *C (S. Typhi and S. Paratyphi A, B,* and C), which are among the more than 2600 closely related Salmonella enterica serovars. A unique set of surface antigens, including flagellar H, virulence-capsule (Vi), and lipopolysaccharide O (somatic), distinguish several Salmonella serovars, such as *S. Typhi* and *S. Paratyphi*. *Salmonella enterica* is divided into typhoidal and nontyphoidal *Salmonella serovars* (NTS) based on host-specificity and disease consequences. Most NTS serovars, which are represented by *S. Typhimurium* and *S. Enteritidis*, can infect both humans and animals and result in a self-limiting gastrointestinal illness. Human salmonellosis, except a few cases where NTS causes invasive illness [7-12]. The infection pathway and certain clinical manifestations are shared by Salmonella serovars, in addition to the difficulties in diagnosing closely related strains. After consuming tainted food or drink, salmonella serovars are spread through the fecal–oral pathway. Enteric fever takes about 8 to 14 days to incubate, and host immune responses, bacterial strains, and dosages all influence how long the illness lasts and how severe it is. Clinically, typhoid and paratyphoid fevers are identical. Although typhoid fever is more common than paratyphoid fever in the majority of endemic locations, they can present with sequelae of similar severity. For example, a clinical-presentation-based diagnosis is challenging because symptoms such high fever, headache, malaise, anorexia, quick pulse, leukopenia, thrombocytopenia, stomach discomfort, and neurological sequelae are not exclusive to enteric fever. Similar symptoms may arise from bacterial (brucellosis, tuberculosis), parasitic (typhus, malaria, leishmaniosis), and viral (dengue, influenza) illnesses that are similarly prevalent in endemic areas. Enteric fever cannot be accurately distinguished from other illnesses with the diagnostic methods available today [13-19]. The advent of extensively drug-resistant (XDR) Salmonella and the global spread of multidrug-resistant (MDR) Salmonella both highlight the need for better diagnostic methods and novel antibiotic-alternative treatment approaches. The main treatment for enteric fever is antibiotics, but Salmonella is constantly changing to become resistant to antibiotics by acquiring plasmid, prophage, transposon, or chromosomal gene changes. Multidrug-resistant (MDR) Salmonella are strains of *S. Typhi* and *S. Paratyphi* that are resistant to all of the first-line antibiotics, ampicillin, chloramphenicol, and co-trimoxazole, according to numerous reports. Enteric fever would be eradicated with the introduction of new diagnostic tests that enable the early detection of S. Typhi and *S. Paratyphi* infection and the identification of chronic carriers. In addition to identifying asymptomatic carriers, ideal diagnostic tests should be able to differentiate the illness from others. A sizable portion of patients who have recovered (2–5%) develop into asymptomatic chronic carriers who may occasionally excrete the bacteria for years. Since *S. Typhi* and *S. Paratyphi* are human-restricted infections with no other known reservoirs, chronic carriers act as a primary reservoir for these viruses, which primarily persist in the gallbladder for local and global transmission. The advantages and disadvantages of the current

enteric fever diagnostic tests, significant bacterial virulence factors in relation to their potential as new diagnostic biomarkers, other bacterial determinants identified by systemic approaches as promising biomarkers, and the ongoing difficulties in finding new ideal biomarkers and tests are all covered in this review [20-25].

The main purpose of the presented manuscript is to provide a brief overview of the relevance of identifying typhoid and paratyphoid A and B pathogens and improving measures for their detection and treatment based on the results of reputable scientific research.

Epidemiology. An estimated 3.8 million cases of paratyphoid fever and 9.2 million cases of typhoid fever occur globally each year, resulting in an estimated 133,000 fatalities. About 450 cases of typhoid fever and 130 cases of paratyphoid fever caused by Paratyphi were verified by culture in 2019 before to the COVID-19 pandemic. A were documented in the United States; between 2020–2021, when COVID-19 affected U.S. travel patterns, there were roughly 150–160 cases of typhoid fever and 30–50 cases of paratyphoid fever caused by *Paratyphi A* annually. There are very few reports of paratyphoid fever brought on by *Paratyphi B* or *Paratyphi C* [3-9]. In the United States, foreign visitors account for over 85% of instances of typhoid fever and 80% of cases of paratyphoid fever; over 70% of these cases involve tourists returning from South Asia, including Bangladesh, India, and Pakistan. Other tourists who have contracted enteric fever have traveled to Southeast Asia, Africa, Latin America, and, less frequently, East Asia and the Caribbean. Visitors to friends and family are more vulnerable because they may not seek pre-travel medical advice or typhoid immunization, and they may be less cautious with food and water while overseas than other tourists. Travelers have contracted typhoid fever during stays of less than a week in nations where the disease is widely endemic, despite the fact that the risk of infection increases with the length of stay [12-18].

Diagnosis Based on Bacterial Culture. Fever ≥38 °C for at least three days and the isolation of bacteria from blood or bone marrow are necessary for the final diagnosis of enteric fever. Bacterial isolation enables us to characterize the pathogen for antibiotic resistance genes and the cause of the disease outbreak in the specific site, while culture continues to be the cornerstone of diagnosis. The approach lacks sensitivity despite having 100% specificity. The quantity of viable bacteria in blood (≤1 CFU/mL) and bone marrow (~10 CFU/mL) is closely correlated with the sensitivity of blood and bone marrow cultures, which are typically ~50% and ~80%, respectively [3-8]. To improve the sensitivity of bacterial-culture-mediated diagnostics, a number of techniques have been used. For instance, adding ox bile or bile salt (sodium taurocholate) to the culture media has boosted the frequency of bacterial isolation in a shorter amount of time. More precisely, bile contents lyse blood cells to release bacteria and inhibit the bactericidal function of blood. Similarly, without altering the overall frequency of isolation, sodium polyethanol sulfonate can likewise lessen the bactericidal activity of blood and minimize the testing time needed for bacteria isolation. Blood clot culture also shows greater sensitivity and fast bacterial growth when serum is removed because of its bactericidal effect. To increase the frequency of bacterial identification and solve the sensitivity problem with culture-based diagnostic techniques, more blood volumes and specimen dilutions with medium have also been employed [12-16]. According to these research, a blood to bacterial culture medium (such as tryptic soy broth, or TSB) ratio of at least 1:10 is ideal. The conventional procedure entails a minimum of one week of incubation at 37 °C and monitoring for bacterial development. As previously mentioned, the gold standard for diagnosing enteric fever is a bacterial-culture-based diagnosis, which also enables antibiotic-susceptibility testing, which is crucial for choosing an appropriate antibiotic treatment plan. The lengthy turnaround time (≥48 h) needed for bacterial growth and identification and the requirement for suitable laboratory infrastructure—which isn't always present in endemic areas—are the main drawbacks of this approach [20-25].

Diagnosis based on the detection of bacterial nucleic acids. Polymerase chain reaction (PCR), which amplifies Salmonella serovar-specific DNA for diagnosis, is used in nucleic acid detection. The

quick turnaround time is this method's main benefit. PCR techniques are useful because they can identify DNA specific to Salmonella that has been recovered from either living or dead bacteria, or both. Antibiotic treatments, which are especially prevalent in some endemic areas, and/or host immune responses can cause dead bacteria in blood. One drawback of PCR techniques is the requirement for specialized equipment and skilled individuals to perform the PCR. Salmonella-specific DNA sequences are amplified after DNA is extracted from patient samples using this technique [4-11]. Flagellin (fliC), Vi polysaccharide (viaB), 16s rRNA, heat-shock protein (groEL), cytotoxin (clyA), and other conserved genes are the most often utilized target genes for the diagnosis of enteric fever. The test's accuracy is typically determined using blood culture results because there isn't a defined reference technique. Numerous investigations have shown that the specificity can be close to 100% when carried out under ideal circumstances, whereas the sensitivity ranges from 40 to 100%. There have been reports of varying sensitivity across a range of technologies, including nested PCR, multiplex PCR, loop-mediated isothermal amplification (LAMP) PCR, quantitative real-time PCR (qRT-PCR), and conventional PCR. However, none of them are unrestricted. A brief culture of blood samples prior to the PCR process (referred to as blood culture PCR [66]) and the removal of background human DNA from blood specimens [65] shown a several-fold increase in sensitivity. In conclusion, compared to their culture-based equivalents, PCR-based techniques are comparatively easier, quicker, and more economical. Sensitivity to illness detection is still a problem for an ideal assay, though [16-23].

Diagnosis by serology. Kauffman-White classification is the basis for the serological identification of S. enterica serovars. Because many of the antigens are shared by various Salmonella serovars, the current serological tests cannot accurately identify enteric fever (specificity is not 100%). Although some of the antigens are shared by various Salmonella serovars, the primary antigens used to distinguish S. Typhi and S. Paratyphi are frequently limited to Vi, lipopolysaccharides (LPS) O, and flagellar H antigens. Consequently, positive results from serological diagnostic tests are suggestive of enteric fever, in contrast to blood-culture-mediated diagnostic techniques. Nonetheless, serological testing is quick and easy, which is very helpful for promptly controlling illness in underdeveloped endemic areas. The linear polymer of α-1,4-2-deoxy-2-N-acetylgalacturonic acid is known as the Vi antigen. The viaB locus, which is a component of Salmonella Pathogenicity Island 7 (SPI 7), contains the genes responsible for the expression regulation (tviA), synthesis (tviBCDE), and transport and localization (vexABCDE) of Vi polysaccharide. The viaA locus contains a global regulator system called rcsABC that controls the synthesis of Vi polysaccharides. Only S. Typhi and S. Paratyphi C (as well as S. Dublin and Citrobacter freundii) have vi polysaccharides; S. Paratyphi A, B, and NTS do not [11-21].

Prospects for the Development of New Diagnostics. We can find a diagnostic biomarker or biomarkers that are appropriate for new diagnostic techniques, with higher specificity and sensitivity tailored for patient circumstances related to vaccination and past infection history, by expanding our knowledge of host–pathogen interactions, with a focus on the bacterial antigens involved, and host responses against the pathogens during various stages of infection. Nearly 90% of the 4700 proteins produced by S. Typhi's roughly 4.8 Mb genome are highly shared with NTS, including S. Typhimurium. The 300–400 genes that make up the S. Typhi unique genome are distinguished by the accumulation of about 200 pseudogenes, which are also present in the S. Paratyphi genome. There are functional homologs of some of these pseudogenes in NTS serovars that are involved in intestinal colonization. This could help to explain why, unlike NTS, typhoidal Salmonella prefers systemic locations [3-10]. By gaining virulence genes found in loci known as Salmonella pathogenicity islands (SPIs), prophages, and plasmids, several pathogenic strains of Salmonella have emerged. A cluster of virulence factors involved in adhesion, invasion, survival, and toxin generation are encoded by a variety of SPIs of different sizes. For instance, several effector proteins and type III secretory systems (T3SSs) are encoded by SPI-1 and SPI-2. While SPI-2 is necessary for the survival and multiplication of bacteria within phagocytes, SPI-1 plays a part in the invasion of bacteria into intestinal epithelial cells.

Typhoidal Salmonella and NTS share many SPIs, while S. Typhi has four comparatively distinct SPIs: SPI-7, 8, 15, and 18. The lack of significant inflammatory reactions in typhoidal Salmonella infections is also probably linked to the bacteria's brief circulation presence and intracellular lifecycle in the reticuloendothelial system throughout the majority of its infectious cycle. Similar to Vi CPS of S. Typhi, which aids in avoiding host innate and adaptive immune responses, a very lengthy O-antigen is present in S. Paratyphi A, which lacks the genes for Vi CPS [14-24].

Discussion. In many low- and middle-income nations, feverish bacterial diseases like typhoid and paratyphoid are prevalent. Due to widespread resistance to earlier, first-line antibiotics, WHO presently advises therapy with azithromycin, ciprofloxacin, or ceftriaxone. various places have various resistance patterns, and these patterns are evolving. Ciprofloxacin use is frequently prohibited in South Asia due to fluoroquinolone resistance. In Pakistan, forms of enteric fever that are very drug-resistant have surfaced. Susceptibility to outdated first-line antibiotics, such chloramphenicol, has reappeared in various parts of the world. The use of azithromycin and fluoroquinolones in the treatment of enteric fever has previously been the subject of a Cochrane Review; however, the use of cephalosporins has not been thoroughly studied, and the best course of action and length of treatment remain unknown [2,3,5,7,11]. Current diagnostic techniques for enteric fever, such as those based on cultures, show excellent specificity but have poor sensitivity and a short turnaround time. Although PCR-based nucleic acid detection techniques are rather quick, they need specialized equipment and skilled workers. The Widal test is an example of a serological approach that has poor specificity and sensitivity but is fast and consequently highly POC-compatible in endemic areas. Several high-throughput techniques have been used to find bacterial and host biomarkers that are relatively distinct for enteric fever and to distinguish between acute, recovery, and convalescent infection stages in order to build the best diagnostic techniques. There isn't enough information at this time to identify a single perfect biomarker. Nonetheless, these findings will provide the foundation for subsequent endeavors. For example, a breakthrough from conventional detection techniques that results in ultrasensitive biomarker detections should be made if we choose to use one or a small number of biomarkers available from the finished procedures [9-14]. A reasonably priced signature biomarker panel that distinguishes enteric fever from other febrile illnesses and healthy/healthy-recovered persons who have previously been exposed to pathogens should be developed if we choose to employ conventional detection techniques. Furthermore, the absence of infrastructure in endemic areas makes the high-end technologies (such as proteomics, transcriptomics, and metabolomics) in question incompatible. As a result, it is necessary to find simpler, less expensive solutions or transform these technology into something more widely available. In actuality, the most crucial element in identifying *S. Typhi* and *S. Paratyphi* infections in endemic areas is locating a low-cost, user-friendly diagnostic tool. Finally, although though it is more difficult, future work should focus on creating diagnostic techniques that identify chronic carriers of these human-specific infections who are healthy or asymptomatic [16-23].

Conclusions. Current diagnostic techniques for enteric fever, such as culture-based approaches, have a high specificity but a low sensitivity and a short turnaround time. Although PCR-based nucleic acid detection techniques are rather quick, they require specialized equipment and experienced workers. The Widal test is an example of a serological approach that has poor specificity and sensitivity but is rapid and consequently highly POC-compatible in endemic areas. Several high-throughput techniques have been used to look for bacterial and host biomarkers that are relatively distinct for enteric fever and to distinguish between acute, recovery, and convalescent infection stages in order to build the best diagnostic techniques.

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