THE MEDICAL, SOCIAL AND ECONOMIC IMPORTANCE OF TYPHOID AND PARATYPHOID FEVER, MEASURES TO IMPROVE THE EFFECTIVENESS OF DIAGNOSIS AND TREATMENT

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ABSTRACT

An estimated 11.9 to 26.9 million episodes of enteric fever occur each year, making it a significant worldwide health concern. Enhancing access to clean drinking water and funding sanitation and hygiene initiatives will be necessary for the long-term prevention of enteric fever. Typhoid Vi-conjugate vaccines (TCVs) have emerged as innovative short-to-medium-term typhoid fever control techniques, providing hope that disease control may be possible soon. The vague clinical presentation of enteric fever and the low sensitivity of widely used tests make diagnosis difficult. Investing in diagnostics could help with vaccination impact studies, enhance management, and improve disease burden estimations. There is a need for a new generation of trustworthy diagnostic tests that are also affordable, accessible, sensitive, and specific. Multidrug-resistant, fluoroquinolone-resistant, and extensively drug-resistant (XDR) strains of Salmonella Typhi have emerged and spread throughout the world, highlighting the significance of ongoing surveillance and proper antibiotic stewardship as part of a global strategy to combat antimicrobial resistance (AMR). In order to guide treatment decisions in the lack of reliable diagnostics and laboratory facilities, current empirical treatment guidelines should be updated to address local

AMR trends. The WHO Strategic Advisory Group of Experts (SAGE) advocated the programmatic use of TCVs in high-burden countries in September 2017. Future and ongoing research should focus on supporting the use of TCVs in high-burden nations and examining the effects of these vaccines in a variety of settings. With the introduction of next generation TCVs, we now have a useful and reasonably priced public health tool that can be used into regular childhood immunization programs for the first time. In order to enhance child health and stop the spread of antibiotic-resistant S. Typhi, we support the use of TCVs in accordance with WHO guidelines in this review.

Introduction. Enteric fever is still a serious public health issue that affects millions of individuals annually and disproportionately affects low- and middle-income nations. The emergence and spread of multidrug-resistant (MDR) and fluoroquinolone-resistant strains of *Salmonella Typhi*, an increase in the incidence of *S. Paratyphi A* infection in South Asia, and the creation of a new generation of typhoid conjugate vaccines (TCVs) are examples of how the global enteric fever landscape has gradually changed over the past 20 years. There is reason for optimism in attempts to control enteric fever worldwide given the recent approval and upcoming deployment of TCVs. However, there are still a number of difficulties. Salmonella enterica serotype infections Enteric fever, which is a combination of typhi and paratyphi, poses a difficult clinical problem for medical professionals all over the world. With topics including epidemiology, pathophysiology, therapy, consequences, patient education, and preventive strategies, this activity provides a thorough overview of these infections [1-5]. Clinicians must understand the subtleties of typhoid and paratyphoid fever in order to identify symptoms including fever, lethargy, anorexia, headache, malaise, and abdominal discomfort. Furthermore, the need for doctors to stay current on the most effective treatment strategies is highlighted by the changing landscape of antimicrobial-resistant bacteria, especially severely drug-resistant forms. *Salmonella enterica serotypes Typhi (S Typhi)* and *Paratyphi (S Paratyphi) A, B,* and C cause typhoid fever and paratyphoid fever, two febrile multisystemic disorders that are clinically identical. Known collectively as enteric fever, the disease causes around 9 million illnesses and 110,000 deaths worldwide each year. In South and Southeast Asia, enteric fever is the most common cause of bloodstream infections acquired in the community. Enteric fever is the second most common cause of serious and occasionally fatal infections among travelers, and it is a sickness that must be reported in the US and many other developed countries. After 6 to 30 days of incubation, enteric fever gradually manifests as a fever accompanied by headache, malaise, anorexia, exhaustion, and abdominal symptoms. Inadequate or delayed therapy may result in intestinal perforation, sepsis, or meningitis. The recent appearance of widely drug-resistant strains has significantly hampered treatment and aroused concerns because *S Typhi* and *S Paratyphi* strains have a history of rapidly gaining antimicrobial resistance due to the widespread use of consecutive antibiotics. The "4 Fs" (fly, fingers, feces, and fomites) are thought to be how *S Typhi* and *S Paratyphi* spread [6-12]. They affect persons who visit or reside in low- and middle-income nations that lack WASH (clean water, sufficient sanitation, and hygiene). Reducing the prevalence of enteric fever and other illnesses

transmitted through the fecal-oral pathway requires improved WASH infrastructure. The "big 3"—malaria, TB, and the human immunodeficiency virus/acquired immunodeficiency syndrome—have historically received more funding and attention than enteric fever. However, attempts to control enteric fever have been redoubled due to the threat of incurable variations. The illness burden has been reduced by WASH programs, better surveillance and knowledge of antimicrobial resistance trends, and recently discovered typhoid conjugate vaccines. The epidemiology, pathophysiology, therapy, management, complications, patient education, preventative strategies, and the role of the interprofessional team in enhancing patient care and lowering the burden of this disease are all covered in this activity. Even though there are a number of obstacles to managing this illness, new developments offer optimism that the effects of enteric fevers may eventually be reduced or eradicated. This course teaches medical professionals the critical role that the interprofessional healthcare team plays in treating enteric fever [13-18]. By utilizing an interprofessional approach, collaboration between doctors, public health specialists, and other healthcare workers improves patient care. Clinicians can improve patient outcomes by cooperating, particularly in low- and middle-income nations where enteric fevers present serious public health issues. The goal of this study is to provide an overview of the current state of enteric fever, with a particular emphasis on the disease's burden, diagnosis, treatment, and prevention. Apart from providing an overview of various recent research developments, our objective is to pinpoint knowledge gaps that may be filled in further investigations [19-24].

The main purpose of the presented manuscript is a brief analysis of the medical, social and economic significance of typhoid and paratyphoid fever, as well as measures to improve the effectiveness of diagnosis and treatment based on the results of reputable scientific papers.

Pathogenesis and disease. The Gram-negative facultative anaerobic bacillus *S. enterica* subspecies enterica serovar typhi *(S. Typhi)* is the cause of typhoid disease. The related organism *S. enterica* subspecies enterica serovar *paratyphi (S. Paratyphi)*, which is separated into three subtypes—*S. Paratyphi A, B,* and *C*—causes paratyphoid fever. Typhoidal Salmonella serovars, which include *S. Typhi* and *Paratyphi*, can cause the clinical symptoms of enteric fever. *S. Typhi* and *Paratyphi* are human-restricted diseases that, in contrast to other *S. enterica* serovars, induce a systemic sickness that, in certain cases, progresses to an asymptomatic chronic carrier state. Consumption of tainted food or water can spread *S. Typhi* and *Paratyphi* by short-cycle or long-cycle transmission. The contamination of food and water in the local area due to poor sanitation and hygiene practices, either by shedding from acute or chronic carriers, is known as short-cycle transmission. Contamination of the larger environment, such as sewage pollution of water supplies or improper treatment of piped water, is referred to as long-cycle transmission. Depending on the epidemiological setting and between *S. Typhi* and *Paratyphi*, the proportional contributions of each route of transmission may change [5-11]. Typhoid fever can appear in a variety of ways, from a moderate disease with low-grade fever and malaise to a severe, potentially fatal systemic sickness with several consequences, such as encephalopathy, intestinal bleeding, and intestinal perforation. A brief interval of asymptomatic primary bacteremia occurs after bacterial ingestion and systemic invasion. Depending in part on the size of the inoculum, the incubation period can vary from 3 to 60 days, although it usually lasts 7 to 14 days. Fever, malaise, anorexia, headache, arthralgia, myalgia, nausea, stomach pain, and dry cough are among the often nonspecific symptoms. Before symptoms appear, there may be

sporadic, asymptomatic bacterial shedding in the feces. High temperature, relative bradycardia, abdominal pain, hepatomegaly, splenomegaly, or rose patches are examples of clinical symptoms. Although field data from the biggest case series to date, which included 609 enteric fever patients in Nepal, indicate that both serovars generate an identical clinical presentation, *S. Paratyphi* may cause a milder illness than *S. Typhi.* About 1–5% of people with acute typhoid illness are believed to develop chronic carriers in the absence of appropriate antibiotic therapy. Gallstones, female sex, advanced age, and insufficient treatment regimens are risk factors for chronic carriage. Chronic carriers may be in charge of sustaining low-level disease transmission, which could make efforts to eradicate the disease through immunization and sanitation initiatives more difficult [13-23].

A burden of illness. In recent years, a number of groups have released research that have increased estimates of the worldwide burden of enteric fever. These studies have included more surveillance data from sub-Saharan Africa and have enhanced our knowledge of the disease's epidemiology by accounting for certain risk factors. An estimated 11.9 to 26.7 million cases and 128,000 to 216,500 fatalities are attributed to the disease each year. The majority of enteric fever cases worldwide occur in low- and middle-income nations. Due to advancements in water quality, sanitation, and hygiene, the disease has virtually disappeared as a public health issue in high-income nations over the past century. The high prevalence of typhoid fever in South and South-East Asia has been a consistent finding of burden-of-disease studies conducted thus far [5-10]. Typhoid epidemiology in these areas is compounded by significant intra- and inter-country variance. For instance, incidence rates ranged from 24.2/100,000 in Vietnam to 493.5/100,000 in some regions of India, according to statistics from the Diseases of Most Impoverished program. Typhoid fever is not limited to metropolitan regions with inadequate sanitation systems, as evidenced by recent studies showing high incidence of the disease in rural areas of West Africa and Cambodia. In Africa, the epidemiology of typhoid disease may be more heterogeneous. The prevalence of blood-culture proved typhoid fever varied from 29 to 247 cases/100,000 person-years in rural and urban areas, according to surveillance conducted in two locations in Kenya between 2006 and 2009. With adjusted rates ranging from 0 in Sudan to 383/100,000 person years in Burkina Faso, recent data from the Typhoid Fever Surveillance in Africa Program revealed significant variations in incidence rates among African sites. Additionally, this study showed significant intracountry heterogeneity, with rural Ghana having higher rates than metropolitan areas. The goal of ongoing surveillance studies, such as the Strategic Typhoid Alliance across Africa program, the Surveillance of Enteric Fever in Asia Project, and the Severe Typhoid in Africa Program, is to improve our knowledge of age distribution, better characterize the burden of severe typhoid disease, and better understand the role of chronic carriers in transmission dynamics. The information gathered from these investigations is expected to contribute to the development of future preventative measures [13-21].

Diagnosis. Enhancing current enteric fever diagnostics and creating a new generation of accessible, affordable, sensitive, and specific assays are still urgently needed. Although bone marrow culture is regarded as the "gold-standard" diagnostic procedure for enteric fever, it is often not feasible to carry out in many endemic environments. The primary method of diagnosing typhoid and paratyphoid is blood culture. According to a recent comprehensive study, blood cultures have an average diagnostic sensitivity of 61.1% [95% confidence interval

(CI) 51.9–70.3%]. Theoretically, clinical algorithms and rapid diagnostic tests (RDTs) for typhoid and paratyphoid fever might be used to distinguish between feverish individuals and direct treatment, especially in places without adequate laboratory facilities. The Typhidot/Typhidot-M test, the TUBEX test, and Test-It Typhoid are the most widely used RDTs for diagnosing enter fever. There is not enough data to justify the exclusive use of the current generation of typhoid RDTs for the diagnosis and treatment of enteric fever, and their sensitivity and specificity have only been found to be moderate in meta-analyses [4-12]. Antibody-in-lymphocyte-supernatant (ALS), another diagnostic in development, has shown good sensitivity and specificity in endemic conditions. Although a number of polymerase chain reaction (PCR)-based techniques have been developed and have shown encouraging results in certain small-scale investigations, there are presently no extensively used and validated assays in general use, and they are still not very sensitive. A pre-enrichment procedure can increase the sensitivity of PCR-based tests. Scalability and widespread adoption of molecular diagnostics and ALS are now hindered by limited laboratory infrastructure, expense, and the time needed to receive results. The use of high-throughput technologies, such as mass spectrometry, next-generation sequencing, and antigen arrays, on clinical specimens is one of the next directions for diagnostic biomarker discovery. Nňström and associates have discovered a group of compounds that may differentiate typhoid from paratyphoid fever and enteric fever febrile, typhoid negative controls, and chronic carriers using mass spectrometry on serum samples from enteric fever patients. Signatures that accurately identify cases of enteric fever could also be found using transcriptional data from people with acute typhoid fever [14-23].

It was thought that between 10 and 30 percent of people died from enteric fever before to the development of antibiotics. Over the past nearly 70 years, the availability of conventional first-line antibiotics (trimethoprim-sulfamethoxazole, ampicillin, and chloramphenicol) has lowered the overall mortality rate to less than 1%. The rise of so-called multidrug-resistant (MDR) bacteria, which are resistant to all three of the "traditional" first-line antibiotics, has unfortunately restricted their usage. IncHI1 plasmids, which carry resistance genes like catA, sul1, sul2, dfrA, blaTEM-1, strA, strB, tetA, tetB, tetC, and tetD on composite transposons, are commonly used to impart resistance in MDR strains. It has also been observed that these MDR-associated genes integrate inside the H58 S chromosome. Typhi in isolates from Bangladesh, Nepal, and India. The 1980s and 1990s saw multiple enteric fever outbreaks caused by MDR strains, which prompted the widespread adoption of fluoroquinolones as first-line treatment. The widespread use of fluoroquinolones has resulted in the establishment of intermediate and completely fluoroquinolone resistant forms of typhoid, despite significant success in treating MDR typhoid [5-11]. Chromosome mutations in the gyrA, gyrB, parC, and parE genes are the primary cause of fluoroquinolone resistance. A single nucleotide polymorphism (SNP) in codon S83F of gyrA will result in a low-level resistance (ciprofloxacin minimal inhibitory concentration [MIC] of 0.125–0.25 mg/l), whereas additional SNPs in gyrA (D87N) and parC (S80I) confer a higher level of ciprofloxacin resistance (MIC 8–64 mg/l). Fluoroquinolone-resistant S may be treated with the monobactam aztreonam. Typhi, especially in those who have a penicillin allergy. Alternative therapies include carbapenems and tigecycline, however there aren't many studies describing their utility for treating typhoid fever, and their high cost may prevent their widespread usage.Combination antibiotic therapy is occasionally used to treat enteric fever, especially when the diagnosis is

unclear, treatment response is sluggish, and susceptibilities are unknown. Combination therapy may lessen the rate at which antibiotic-resistant bacteria arise and have synergistic effects. As of right now, there is little data from randomized trials to support this strategy [12-18]. It may be necessary to combine medication and surgical treatments for chronic carriage. Fluoroquinolones are frequently used to treat chronic carriage, and over 80% of individuals can be cleared with a 28-day course of ciprofloxacin (750 mg twice daily) or norfloxacin (400 mg twice daily). With treatment success rates ranging from 87 to 100% in published research, shorter courses (14 days) of fluoroquinolones may also be effective in treating chronic carriage. Although this has not been properly investigated in randomized controlled trials, a longer azithromycin treatment course (28 days) may be helpful in the management of chronic carriers infected with fluoroquinolone-resistant isolates. When cholelithiasis is present, cholecystectomy may be necessary; concurrent antibiotic therapy is likely to increase the effectiveness of this procedure. Praziquantel antiparasitic therapy is recommended for patients with concurrent Schistosoma infections in order to address persistent intestinal and urine carriage [19-23].

For more than 150 years, it has been known that contaminated drinking water plays a major role in the spread of typhoid disease. Reducing the worldwide burden of typhoid fever will need investments in sanitation and hygiene programs along with access to clean, safe drinking water. In the near to medium term, vaccination is a top priority due to the ongoing high disease burden and the establishment of drug-resistant strains of S. Typhi. The Ty21a and Vi-polysaccharide vaccines have shown efficacy at two years of 58% (95% CI 40–71%) and 59% (95% CI 45–69%), respectively, however their usage in the youngest age group of children is restricted because of their weak immunogenicity and administration discomfort. In Asia, school-based campaigns and vaccination delivery methods utilizing the current healthcare system have been successful in terms of coverage and cost-effectiveness. Compared to previous generations of typhoid vaccines, TCVs, in which Vi-polysaccharide is covalently bound to carrier proteins, have a number of potential advantages. The ability of Vi-conjugate vaccines to elicit immunological responses in newborns, their improved immunogenicity in terms of antibody quantity, quality, and persistence, and the possibility of enhancing immune responses with revaccination are what make them appealing [4-11]. Trials of a prototype Vi-rEPA vaccine, which showed efficacy of up to 91% (95% CI 77–97%) at 2 years when given as a two dose schedule in 2–5 year old children, are the main source of proof-in-principle of TCV efficacy. The Vi-rEPA vaccine has not yet been commercialized, although it proved effective for at least five years and compatible with coadministered expanded immunization programs. TypbarTCV, a Vi-tetanus toxoid conjugate vaccine produced by Bharat Biotech (Hyderabad, India), is the most sophisticated TCV. This vaccine shows better immunogenicity than a Vi-polysaccharide vaccine and is safe and immunogenic in infants as young as six months of age. Significantly, depending on the efficacy endpoint, TypbarTCV has shown efficacy ranging from 54.6 to 87.1% in a rigorous controlled human infection paradigm. Based on serological data, modeling studies have calculated an 85% vaccination effectiveness for TypbarTCV. Depending on the intervention method employed and at a low vaccine cost (about $2 per dose), cost-effective models suggest that routine newborn TCV vaccination is likely to be cost-effective in medium- or high-incidence settings. Three-phase IV efficacy trials carried out as part of the TyVAC consortium and an impending introduction of TCV in Navi Mumbai, India, will produce

additional safety and immunogenicity data. Many of the TCVs under development, such as VI-DT, Vi-rEPA, Vi-CRM197, and Vi-tetanus toxoid conjugates, have finished Phase 1 and 2/3 studies [13-18]. The WHO Strategic Advisory Group of Experts on Immunization advised the programmatic use of TCVs in typhoid-endemic nations in October 2017. The recommendations centered on the use of TCV as a single dose starting at age 6 months, as well as programmatic delivery in conjunction with other childhood vaccinations. Additionally, catch-up vaccination up to the age of 15 was advised when possible and supported by epidemiologic data. The position paper emphasizes that nations with high incidences of AMR or typhoid fever should prioritize rolling out TCVs. Typhoid control is gaining momentum thanks to the availability of efficient instruments and the backing of important stakeholders. Supporting access to typhoid vaccines where they are most needed is currently the community's biggest challenge [1-7].

Discussion. Salmonella enterica subspecies serovars *Typhi* and *Paratyphi A, B*, and *C* are gram-negative bacteria in the Salmonella genus that cause typhoid and paratyphoid fever, also referred to as enteric fever. These infections are primarily spread by ingestion of contaminated food or water and entry into open wounds. Common infectious diseases like typhoid and paratyphoid fever continue to be a major burden, particularly in some low-income nations. Public health policies will benefit from an examination of the burden of typhoid and paratyphoid fever, even though it has declined globally over the previous three decades. The goal of this study is to thoroughly assess the national, regional, and worldwide burden of typhoid and paratyphoid, as well as the temporal patterns, while investigating any correlations with sociodemographic development over a three-decade period (1990–2021). The Global Burden of Disease (GBD) study was used to assess data on paratyphoid and typhoid fever in 2021. In order to show temporal trends in typhoid and paratyphoid fever incidence, mortality, and disability-adjusted life years (DALYs) from 1990 to 2021, we performed calculations. By examining the most recent GBD database, our study carried out a thorough and methodical evaluation of several typhoid and paratyphoid fevers at the international, regional, and national levels [1,2,4,11]. In addition to concentrating on morbidity, mortality, and disability-adjusted life years, it may properly and thoroughly depict the distribution of disease burden and health status among individuals across various geographical areas. Additionally, we carried out in-depth investigation and continued to group by age, sex, and country region, offering a comprehensive viewpoint for comprehending the state of global health. Our global estimates of the typhoid fever burden are essentially in line with earlier estimates, but they provide crucial details regarding the burden's geographic distribution and the respective contributions of paratyphoid and typhoid fever. The necessity for more thorough active surveillance of typhoid and paratyphoid fever is highlighted by the stark disparities between reported burden estimates in some areas, which are caused by a lack of data. Our research can help prevent and cure typhoid and paratyphoid fever by offering a more comprehensive, multifaceted understanding of the illness. The current study showed declining trends in the incidence, mortality, and DALYs of typhoid and paratyphoid fever over the last three decades [8,11,12]. These changes are mostly attributable to the promotion and upgrading of vaccinations as well as the improvement of sanitary conditions in different locations. These results demonstrated that cost-effective preventative and control strategies were still necessary to lessen the incidence of typhoid and paratyphoid fever, particularly in impoverished areas. Despite tremendous progress, typhoid and paratyphoid fever still constitute a serious hazard, leading

to high rates of death and disability. Furthermore, the possibility of medication resistance developing and spreading still warrants ongoing attention. Important tactics to successfully fight typhoid and paratyphoid fevers include improving food, water, and sanitation conditions, encouraging immunization campaigns, and funding research and development [12-22].

Conclusions. Poverty-related illnesses include paratyphoid fever and typhoid. Enteric fever is still a serious public health issue in settings with low resources, despite being all but eliminated in the affluent world. There are still a number of difficulties, such as in the areas of diagnosis, illness epidemiology, and treatment. The dynamic antibiotic resistance profiles of *S. Typhi* and *S. Paratyphi,* including the establishment of cephalosporin resistance and the apparent reemergence of strains susceptible to conventional first-line drugs, must be continuously monitored. Novel antimicrobials, adjuvant therapy, antibiotic cycling, and combination medicines are among the treatment approaches that need more research.

Typhoid control has advanced significantly with the discovery and upcoming introduction of scalable, affordable TCVs, which may significantly reduce the disease's worldwide burden. TCVs have the potential to be a useful tool that addresses some of the drawbacks of current typhoid vaccines and, for the first time, provides a vaccine that can be routinely used in childhood immunization programs. A WHO-prequalified TCV is effective in a controlled human infection model, and earlier generation TCVs have demonstrated great efficacy in field settings. With policy, regulatory, and financial support from important parties like WHO and Gavi, there is now enough evidence to warrant the implementation of TCVs in the field.

The effects of these vaccinations will be investigated in a variety of settings through ongoing research, including that carried out by the TyVAC collaboration.In the past, a number of chances to control typhoid have been lost. Since 2001, TCV efficacy statistics have been available, but a number of obstacles have prevented these encouraging findings from being expanded upon. Furthermore, there was very little adoption of the 2008 WHO guidelines for the programmatic deployment of the Ty21a and Vi-polysaccharide vaccines. Millions of people still contract typhoid every year, no new diagnostics have been developed, and antibiotic resistance has gotten worse. We support the use of TCVs in accordance with WHO guidelines to enhance child health and stop the spread of antibiotic resistance in order to learn from the past.

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