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Perspective

Toward Typhoid Fever Elimination

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A B S T R A C T

Salmonella enterica serotype Typhi (*S* Typhi) causes typhoid fever and is responsible for an estimated 9 million cases and 110,000 deaths globally per annum. Typhoid fever is endemic in areas where water, sanitation, and hygiene (WaSH) infrastructure is poor. Serious complications develop in approximately 10%-15% of patients if left untreated, and this is driven by inadequate diagnostic methods and the high burden of antibiotic-resistant strains, complicating clinical management and ultimately prognosis. Asymptomatic chronic carriers, in addition to acutely infected patients, contribute to continued transmission through the shedding of the organism in the feces. The high morbidity and mortality of typhoid fever in low- and middle-income countries reinforce the need for an integrated control approach, which may ultimately lead to elimination of the disease in the 21st century. Here we discuss the challenges faced in pursuit of typhoid fever elimination.

Unknown burden of disease

The global burden of typhoid fever presently stands at 9 million cases and 110,000 deaths annually 2020(Institute for Health Metrics and Evaluation, 2020). However, only limited population-based surveillance data for blood culture–confirmed typhoid are available from Asian and African countries, which are necessary for estimating the true burden of the disease (Ochiai et al., 2008). Although the largest burden of typhoid fever exists among children in Africa and South and Southeast Asia, there are regional differences both within and between countries (Mweu and English, 2008; Radhakrishnan et al., 2018). Therefore, knowing the updated burden of typhoid fever at the global, national, and regional level is essential to successfully introduce typhoid conjugate vaccines (TCVs). The necessity for updated incidence data was also stressed by policy makers of different African and Asian countries before the introduction of TCVs into the Expanded Program on Immunization (EPI) (DeRoeck et al., 2005). A robust population-based surveillance system will help to reveal the hotspots of disease transmission and high-risk groups that need to be vaccinated.

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Diagnostic needs

Isolation of *S.* Typhi from bone marrow or blood is recommended by the World Health Organization (WHO) for a confirmatory diagnosis of typhoid fever (WHO, 2003). Bone marrow culture is considered the gold standard for diagnosis. However, bone marrow aspiration is not commonly practiced because of its invasive nature. Thus, blood culture is the mainstay of diagnosis, although its sensitivity is approximately 40%-87% (Crump et al., 2015). Other diagnostic methods including Widal (81.5% sensitivity; 18.3% specificity), TUBEX (60% sensitivity; 58% specificity), and Typhidot (67% sensitivity; 54% specificity) tests show poor sensitivity and specificity in diagnosing typhoid fever (Mawazo et al., 2019, Naheed et al., 2008, Valones et al., 2009). Usually, patients with typhoid fever are diagnosed on the basis of clinical judgment in Asia and Africa, although the presenting signs and symptoms are not distinguishable from those of other febrile illnesses (Kariuki, 2008, Ochiai et al., 2008).

A major challenge in diagnosing typhoid fever in endemic countries is the lack of laboratory technicians and infrastructure, where the disease burden is estimated using uncertain denominator by governments and/or hospitals. Microbiology laboratories, with appropriately trained personnel, as well as evaluation of novel diagnostic methods are required in endemic countries to determine the burden of disease and to plan control strategies accordingly.

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High burden of antimicrobial resistance/extensively drug-resistant strains

Patients with severe typhoid disease, including those with gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy, are typically hospitalized and treated with antibiotics after conducting susceptibility testing, but most patients (60%-90%) in endemic countries are managed at home with empirical antibiotic treatment, without a definitive diagnosis (Parry et al., 2002). This excessive and irrational use of antibiotics has placed a selective pressure on the organism, which ultimately led to antimicrobial resistance (AMR). A high rate of multidrug-resistant *S.* Typhi (e.g., chloramphenicol, ampicillin, and cotrimoxazole) was observed in different parts of Asia and Africa with reduced susceptibility to fluoroquinolone reported in ~70% of cases. Resistance to third-generation cephalosporins and azithromycin has recently emerged in low- and middle-income countries (LMICs), such as Pakistan, India, and Bangladesh. Outbreaks of extensively drug-resistant (XDR) *S.* Typhi strains (resistant to first- and second-line antibiotics as well as third-generation cephalosporins) in Pakistan have highlighted the dangers of improper and unnecessary use of antibiotics and the threat of being left without any treatment options for patients with typhoid fever (Saeed et al., 2019). In addition to strict regulations for monitoring antibiotic rollout, policies to reduce the existing prevalence of AMR and prevent its further development have been developed and implemented at the national level in many countries, including Canada, the United States, European countries, China, South Korea, and Taiwan. The policies include information on the preferred use of antibiotics for healthcare workers and recommendations for vaccination. However, most LMICs have yet to implement these policies (Rogers Van Katwyk et al., 2019).

Asymptomatic carriers

After recovery from acute illness, approximately 2%-5% of patients develop a carrier state and continue shedding the organism in their stool for up to 1 year (Parry et al., 2002). To interrupt this transmission and to reduce the disease burden, it is important to identify and treat carriers who are believed to be the main source of transmission in the community. Microbiological culturing and isolation of *S.* Typhi from bile, gallbladder stones, or tissue after elective cholecystectomy is the gold standard for diagnosis of chronic carriers; however, it is not broadly used. The currently available diagnostic methods such as anti-Vi immunoglobulin G antibody titer, microbiological culturing of duodenal specimens, and consecutive stool and urine specimens have low sensitivity and thus low utility for the diagnosis of carriers at scale. Fluorescent antibody techniques and polymerase chain reaction have been used; however, they were less successful in detecting chronic carriers.

Urban slums and climatic influences

The risk of transmission of *S.* Typhi among people who have no access to safe water is twice that of those who have such access (Mogasale et al., 2018). Rapid urbanization and lack of proper waste disposal systems cause fecal contamination of the urban environment (Amin et al., 2019). As a result, open sewage that flows just outside the doors of homes in urban slums enters into the homes during the rainy season and contaminates the domestic water source (Ross et al., 2020), which may increase the risk of typhoid transmission. Despite this knowledge, it is difficult to provide better WaSH options for 'informal' urban slums because the land is not formally recognized by the governments of LMICs. For 'formal' slums, evidence-based WaSH interventions are currently lacking, and most LMICs appear unwilling to make large financial investments to improve the lives of slum dwellers. The combination of WaSH interventions with health education and vaccination against different enteric diseases has helped in controlling outbreaks. However, establishment of infrastructure for waste and sewage disposal systems and for ensuring an uncontaminated water supply is dependent on financial capital and, most importantly, political will.

Global warming is likely to increase typhoid transmission and the incidence of the disease (Saad et al., 2018). However, data from a study conducted in Blantyre, Malawi demonstrated that a reduced relative risk for typhoid fever was associated with the highest rainfalls (Thindwa et al., 2019). The study has also reported a bimodal pattern, with increased risk of typhoid at both lower (19°C) and higher (25°C) temperatures compared with the mean temperature (23°C). A lower incidence of the disease was found with extremely hot temperatures (>28°C) (Thindwa et al., 2019). A detailed analysis of the spatial and temporal distribution of typhoid fever has shown that the number of typhoid cases increases during the monsoon season in Dhaka, Bangladesh (e.g., 45%, 30%, and 25% during the monsoon, pre-monsoon, and post-monsoon seasons, respectively) (Dewan et al., 2013). Comprehensive analyses of blood culture confirmed that typhoid data and meteorological data are needed in endemic countries to help better predict the seasonal patterns of the disease.

Challenges in implementing vaccination programs

Typhoid vaccines have been available since 1896 for implementation as a short-term control measure. Economic and epidemiological data analysis from the urban sites of India, Pakistan, Indonesia, and Vietnam showed the cost-effectiveness of typhoid Vi vaccination programs for children and adults. More specifically, the result showed that the community-based vaccination programs would be cost-effective in children where the incidence of typhoid fever is high (Nelson et al., 2016). However, typhoid vaccination has not been introduced into the routine immunization programs of many endemic countries with high disease burden, including Bangladesh (161 per 100,000 person-years of observation), Nepal (74 per 100,000 person-years of observation), and Malawi (58 per 100,000 person-years of observation) (Meiring et al., 2021). In response to the large outbreaks of XDR *S.* Typhi strains, Pakistan introduced the WHO-recommended TCV into their routine Immunization Program in November 2019 (Akram et al., 2020). Liberia became the first country in sub-Saharan Africa to introduce TCVs with a national campaign followed by routine immunization in April, 2021 (Shakya et al., 2021). Zimbabwe launched a large integrated national vaccination campaign with the TCV, human papillomavirus vaccine, and inactivated polio vaccine in May, 2021 (Birkhold et al., 2021). It is hoped that other endemic countries will follow in combating AMR outbreaks and reducing the burden of typhoid fever.

There are several crucial factors that hinder TCV implementation in endemic areas. Lower immunogenicity in infants and young children and short duration of protection are the main drawbacks of the licensed injectable Vi polysaccharide and the oral live-attenuated Ty21a vaccines. These challenges are expected to be overcome with the new generation of TCVs. If TCV achieves the target of higher immunogenicity and longer duration of protection, it will be integrated as a short- to medium-term preventive measure. Governments must also prioritize the vaccine for introduction within their EPIs to minimize the programmatic costs of potential roll-outs.

Conclusions

High disease burden and emergence of antibiotic resistance in *S.* Typhi strains, including multidrug-resistant and XDR strains, in endemic countries pose a significant threat for many LMICs. Integrated control including WaSH, effective treatment, health education, point-of-care diagnostics, and vaccination will be required to achieve elimination in the 21st century. Unfortunately, there are still many challenges to make this a reality.

Ethical Approval statement

No ethical approval was required.

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Conflict of Interest

The authors declared no conflict of interest.

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