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SUPPLEMENT ARTICLE

Challenges and Opportunities for Typhoid Fever Control: A Call for Coordinated Action

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The burden of enteric fever caused by *Salmonella enterica* serovars Typhi and Paratyphi is substantial and has high impact in toddlers and young children. This burden is relatively well documented in Asia, and this supplement provides new data on the substantial burden in several sub-Saharan African countries. Challenges in standardized surveillance and imperfect diagnostic tools have resulted in patchy local disease data, which are not well acknowledged or integrated into local country evidence and health awareness for decision making. There is a need to strengthen diagnostics for the generation of burden data in country. Furthermore, the guidelines and training for treatment of enteric fever cases in Africa are sorely needed to help mitigate the inappropriate use of antimicrobial treatment. Classic water safety and access to sanitation development remain powerful tools for the control of typhoid fever, yet the huge economic costs and long timelines are unlikely to provide a short- to middle-term solution. Emerging threats, including multidrug resistance and increasing urbanization in regions such as sub-Saharan Africa, warrant focused attention to shorter-term interventions including immunization, and must include vaccine strategies with the new typhoid conjugate vaccines.

Keywords. enteric fever; typhoid conjugate vaccines; Africa; MDR; WSH.

Enteric fever, caused by the bacterium *Salmonella enterica* serovars Typhi and Paratyphi, has a long history and impact on human lives. Historical records teach us a great deal about typhoid fever—the high disease burden and deadly consequences of the disease; the major routes of transmission; and the potential impact of vaccines. As early as 430 BC, a pernicious plague annihilated half the population of Athens, bringing to an end the "Golden Age of Athens," and is now believed to have been typhoid fever based on DNA examination of dental pulp [1]. Typhoid fever is also credited with causing the deaths of several well-known historical figures, including, putatively, Alexander the Great and, almost certainly, former US President William Henry Harrison [2]. "Typhoid Mary" has become synonymous with the spread of the disease for more than a century [3], and William Budd, an English physician, demonstrated that typhoid fever could be transmitted through water sources in the 1870s [4]. Thus, the person-to-person spread of the disease through food handling or via contaminated water has been documented for >100 years. Furthermore, early reports from the Anglo-Boer War of 1899–1902 demonstrated the ability of the existing inactivated vaccine to protect British troops in South Africa, where vaccination with the killed whole cell vaccine was voluntary and, due to the reactogenic nature of the vaccine, not a popular intervention by the troops [5].

Our long understanding and fear of typhoid fever notwithstanding, many challenges and opportunities persist today for the control of enteric fever in vulnerable human populations.

DISEASE BURDEN IS HIGH

The disease still causes a devastating burden in many low- and middle-income countries, with recent estimates of global incidence ranging between 11.9 million [6] and 26.9 million [7] cases per year, and mortality estimates ranging between 129 000 and 161 000 annually [6, 8], based on an assumed case fatality rate of 1%.

A significant contribution to our understanding of the burden of typhoid and paratyphoid comes from studies conducted in Asia through the Diseases of the Most Impoverished (DOMI) project, which was conducted by the International Vaccine Institute between 2000 and 2008 with support from the Bill & Melinda Gates Foundation. The DOMI project focused on typhoid as well as cholera and shigellosis, and generated considerable data from 7 focal countries: Bangladesh, China, India, Indonesia, Pakistan, Thailand, and Vietnam. For typhoid, the DOMI project highlighted many epidemiological features of the disease in Asia, specifically showing the existence of a high burden of disease in both school-aged and preschool-aged children across sites; the alarming spread of antibiotic resistance; and the potential to target vaccination programs to high-risk settings efficiently, including school-based programs [9, 10].

Prospective disease burden studies found annual incidence rates of blood culture–confirmed typhoid fever of 180–494 per 100 000 among 5- to 15-year-olds in 3 urban slums (North Jakarta, Indonesia; Kolkata, India; and Karachi, Pakistan).

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Furthermore, preschool children aged 2–4 years were also shown to be highly vulnerable with incidence rates that were just as high, ranging from 149 to 573 per 100 000 in these same 3 settings [9]. More recent studies from the region do not indicate any dramatic declines in the incidence of enteric fever, although there is increasing evidence of the burden of paratyphoid fever disease in Asia [11].

By contrast, the relative paucity of sound epidemiological data for invasive *Salmonella* in sub-Saharan Africa led the World Health Organization (WHO) to recommend a continent-wide, standardized approach for collecting accurate incidence and antimicrobial susceptibility data [12]. In 2009, the Bill & Melinda Gates Foundation funded the International Vaccine Institute to conduct the Typhoid Surveillance in Africa Program (TSAP), a multicountry surveillance study aimed at bridging knowledge gaps on the population incidence of typhoid and invasive nontyphoidal *Salmonella* infections in sub-Saharan Africa. As reported in this supplement, and contrary to the previously held belief that typhoid in Africa constituted a relatively modest burden, the results show that in many of the African sites, incidence is as high as that observed previously in Asia, with ranges up to 383 per 100 000 person-years in Burkina Faso, for instance. In addition, the age distribution and the urban/rural distribution of burden vary significantly across the continent, as described elsewhere [13].

DIAGNOSTIC CHALLENGES REMAIN A HURDLE

Despite these data, it is clear that many countries remain uncertain of their true enteric fever disease burden due to the lack of local surveillance or systematic hospital-based surveillance; this is largely compounded by the lack of accurate and inexpensive rapid diagnostic tools, infrequency of laboratory testing, poor disease reporting systems, and the fact that the clinical diagnosis of the disease is often compounded by the occurrence of other febrile illnesses, such as malaria or dengue fever. Accurate and rapid diagnosis of typhoid fever could significantly improve management of cases with reliable antibiotics to which *S.* Typhi or *S.* Paratyphi are sensitive [14]. Furthermore, there is a need for different types of diagnostic assays including the "point of care" assays, which should be sensitive and specific and yield a rapid result for treatment options to the physician. For instance, surveillance diagnostics are required for generating data on the epidemiological parameters of the disease and circulating strains for local evidence generation, awareness, and decision making, whereas environmental surveillance in a region or district could support targeted interventions, such as water and sanitation options, social mobilization and awareness, and immunization strategies. Finally, specific diagnostics are required for the identification of long-term carriers, to support food safety and focused treatment regimens. Each of these needs will require a specific diagnostic assay with different characteristics.

The definitive diagnosis of typhoid fever depends on the isolation of *S.* Typhi from blood, bone marrow, or a specific anatomical lesion. Blood culture is the current reference standard for diagnosis, but has several limitations including the volume of blood required (2–4 mL from toddlers and 10–15 mL from adolescents and adults) due to low levels of bacteremia [15]; delayed transport to the laboratory; prior antibiotic use; limited laboratory expertise and equipment; and expense. The results are only available after 48 hours, limiting physician utility for case management and thus for requesting the test in the first place. Sensitivity of blood culture is estimated to be between 40% and 60% compared with bone marrow culture. Several efforts to improve the yield of blood cultures have been developed including various broth enrichment strategies, automated laboratory equipment, cell lytic media for release of intracellular *S.* Typhi, and increased incubation periods [16], none of which dramatically enhance the sensitivity of blood culture.

Serological assays, primarily the Felix–Widal test, which measures agglutinating antibody levels against the O and H antigens, are poorly sensitive or specific, and have been largely dismissed as an effective diagnostic tool. However, they are cheap and still widely used in developing countries despite low utility. Rapid diagnostic tests for the identification of *S.* Typhi bacteria are desirable and several are available; unfortunately, they are also not sensitive or specific and are therefore not useful for diagnosis and treatment [17]. Polymerase chain reaction–based assays are also increasingly available, yet despite early optimism, have failed to meet the challenges of a rapid, reliable, specific, and sensitive diagnostic [18] and require advanced laboratory equipment and technical expertise, which tend to be available only in central higher-end laboratories. Work is under way to develop improved, simple, robust, and field-usable diagnostics as described by Andrews et al [14], but challenges still exist in this important area and continue to impede progress in the identification and management of enteric fever.

ANTIBIOTIC RESISTANCE IS INCREASING AND MORE THREATENING THAN BEFORE

Multidrug resistance of *S.* Typhi and *S.* Paratyphi strains to the 3 first-line classes of antibiotics (chloramphenicol, ampicillin, and cotrimoxazole) has been well documented, including in Africa [19, 20]. Resistance to the fluoroquinolones, the preferred drug of choice in Asia for multidrug-resistant (MDR) *Salmonella* strains, is growing and has also been reported from the African continent [21]. Infection caused by the MDR strains has been documented to be associated with more severe illness and higher rates of complication and death [12], and with a higher rate of prolonged asymptomatic carrier status [22]. Invasive nontyphoidal salmonellae, which are commonly reported from sub-Saharan Africa, have also shown increasing resistance to antibiotic treatment, as described by Kariuki et al [20].

Potentially even more worrying are the recent reports from Zambia and Malawi that the H58 haplotype has emerged in sub-Saharan Africa and is strongly associated with multidrug

resistance [21, 23]. Furthermore, the H58 multidrug resistance genetic region is integrated into the bacterial chromosome and is not carried on a plasmid. This potentially poses an increasing threat to our ability to treat the prevalent circulating *Salmonella* strains with existing antibiotics and is likely to impact our available front-line drugs very quickly. In the preantibiotic age, case fatality rates for untreated typhoid were high and reaching 10%–15%, indicating an urgent need to tackle this problem.

ENTERIC FEVER CONTROL BY WATER, SANITATION, AND HYGIENE

Since the early recognition of the role of water in the transmission of typhoid fever [4], it has been demonstrated that improvements in access to clean water and improved sanitation result in dramatic reductions in typhoid fever–related death rates in many settings. Furthermore, safe drinking water and sanitation have been declared a human rights issue by the international community, due to their importance in human health [24]. It is clear that as access to safe water and improved sanitation are being developed, this should dramatically reduce the exposure to *S.* Typhi and *S.* Paratyphi bacteria in the environment and, thus, enteric fever disease. However, global progress toward universal access to both safe water and improved sanitation at the household level where the health benefits are optimal are inadequate [25], and are likely compounded by several factors including inequity in coverage, where the most vulnerable populations have the poorest access; increasing urbanization; and increasing water scarcity in many regions. An earlier report indicated that the costs of universal access were approximately US$35 billion per year for sanitation and US$17.5 billion for drinking water per year from 2010 to 2015 [26].

Finally, the impact of improved latrine coverage in Odisha, India, was marginally associated with improved diarrhea rates in young children <5 years of age [27]. The intervention also had only marginal impact on the fecal contamination of water stored in the household, which might have been due to insufficient coverage and use of the latrines at the household level. Nevertheless, this is a disappointing result supporting similar outcomes observed in another state in India [28]. Finally, a recent study in Bangladesh showed that behavioral interventions to improve water quality and personal hygiene gave limited additional protection against cholera when compared to vaccination alone [29]. This should raise the question of whether there is a case for the public health use of typhoid vaccines in an integrated approach for the control of enteric fever.

ARE VACCINES A PREVENTIVE MEASURE FOR TYPHOID FEVER CONTROL?

There has been interest in typhoid fever vaccination for several decades, and although there has also been progress in developing control solutions for typhoid, this progress has been somewhat stilted in many regions. The first vaccine, an inactivated whole cell vaccine, was in use for >100 years, mostly in British and US military populations, but was deemed too reactogenic for continued use [30]. Currently, 2 typhoid vaccines are internationally licensed and have been shown to be safe and efficacious in individuals >2 years of age.

The first is an oral vaccine based on a live attenuated *S.* Typhi Ty21a strain, which was developed in 2 formulations: enteric-coated capsules and a liquid presentation [12]. The commercially available enteric-coated capsules are intended for use in children >5 years of age and adults (orally administered as a single dose every other day). In randomized clinical studies in Chile, the 3-year accumulative efficacy of 3 doses of the vaccine was 67% against blood culture–confirmed typhoid, and 62% protection was shown at 7 years of follow-up [31, 32]. A fourth dose of the enteric-coated capsules gave better protection [33], resulting in the approval of this schedule in the United States, although other countries have licensed the 3-dose regimen. Similarly, the liquid presentation of the vaccine was also shown to be significantly more protective in Chile and Indonesia, and had the added advantage of protecting young children at 3 years of age [31].

The second is a single-dose injectable Vi capsular polysaccharide (Vi-PS) vaccine, which has been developed by several manufacturers, and at least 1 of which is prequalified by the WHO for use in subjects >2 years of age [25]. The vaccines confer protection approximately 7 days postimmunization. As is typical for polysaccharide vaccines, they do not induce protective immune responses in children <2 years of age [12]. In randomized clinical studies in South Africa, the Vi-PS vaccine showed 64% clinical protection at 21 months' duration, declining to 55% after 3 years, although >50% of these school-aged children had protective levels of antibody 10 years after immunization [34, 35]; in Nepal, in 5- to 44-year-olds, 72% protection was shown at 17 months of follow-up [36]. Finally, indirect herd protection of Vi-PS vaccination was demonstrated in a cluster-randomized effectiveness study in Kolkata [37].

Neither product has been widely used, particularly in highly endemic, low-resource settings, given the challenges associated with administration regimens and relatively short duration of protection, which would necessitate periodic boosting. In addition, neither vaccine confers protection or is recommended in children <2 years of age [12]. Several countries in the Asian region have national plans for limited implementation of typhoid vaccines, although the vaccines are widely available in the private market. In 2011, Nepal conducted a large school-based immunization program with the Vi-PS vaccine, demonstrating the feasibility of such a program [38], and, when coupled with the earlier efficacy data shown in Nepal, a national recommendation was made to expand immunization to all school-aged children. Both China and Vietnam have utilized millions of doses of locally produced vaccine since the late 1990s, with demonstrated declines in reported enteric fever cases. The widespread use

of Vi-PS vaccines was also serendipitously accompanied by improvements in water and sanitation in both settings, showing the power of the combined approach. In addition, several other countries have national policies targeting high-risk groups such as food handlers (Brunei, Malaysia, Republic of Korea, and Sri Lanka), and Delhi, India, has also implemented typhoid fever immunization regionally.

Typhoid conjugate vaccines (TCVs) are expected to overcome many of the challenges associated with these previous vaccines, providing higher efficacy, earlier administration to infants and young children at risk, and a longer duration of protection; the ability to be administered in combination with other routine childhood Expanded Programme on Immunization vaccines is an added bonus for programmatic implementation in younger children. A 2-dose Vi-rEPA conjugate vaccine was developed by the US National Institutes of Health, where Vi-PS is conjugated to a novel carrier protein consisting of recombinant exotoxin of *Pseudomonas aeruginosa* [39], and demonstrated 91.5% protective efficacy among preschool children aged 2–5 years in Vietnam, but this vaccine has not yet been licensed internationally [40].

A number of alternative TCV candidates are in development, including a product licensed in India in 2015 (Typbar-TCV, Bharat Biotech International Ltd) that may be eligible for WHO prequalification. This vaccine is the likely lead candidate for evaluating the full public health impact of a TCV, with the potential for widespread programmatic implementation in India, and is the likely lead candidate for WHO prequalification. Another TCV developed by Sclavo Behring Vaccines for Global Health, conjugated to CRM_{197}, was evaluated in two phase 2 immunogenicity and safety studies in adults, young children, and infants in Pakistan and India and in the Philippines, showing safety in infants. The immunogenicity results were disappointing, showing short-lived antibody responses and no immune response to a booster dose [41]. The candidate is under further investigation to elucidate these results. These vaccines, and others in the pipeline [42], will make the reality of the Gavi vaccine subsidy for endemic countries a reality.

GLOBAL PUBLIC HEALTH IMPACT

For a disease that has been well known throughout history and has been successfully addressed in many countries through developments in infrastructure, water and sanitation, and food safety, it is disconcerting to see the relative lack of progress in other parts of the world. These new data from sub-Saharan Africa further underscore the severity of the problem and the need for coordinated action.

In 2008, the WHO reviewed the currently available live attenuated (Ty21a) and Vi-PS vaccines, which had demonstrated significant public health impact in several studies in Asia [10] and Latin America [32], and recommended the use of the vaccines, stating that "[i]n view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of the 2 licensed vaccines (Vi-PS and Ty21a), countries should consider the programmatic use of typhoid fever vaccines for controlling endemic disease" [12]. Despite this recommendation, the strong evidence for the burden of disease, and the prequalification of a Vi-PS vaccine by the WHO in 2011 (Typhim-Vi, Sanofi Pasteur, France), there has been underwhelming uptake of the Vi-PS vaccines.

That same year (2008), the Gavi board reviewed the investment strategy for typhoid fever vaccines. Although the commitment to support typhoid vaccines was made, the decision from the board was to wait for the second-generation TCVs to become available. This was an unprecedented decision—financial commitments for future vaccine subsidy support for a product not yet available—and although it has maintained confidence in future funding availability to support the introduction of TCVs, it has also arguably sent mixed messages for the utilization of the currently available vaccines. Although there have been development delays in the projected TCV pipeline, progress is now becoming evident and, to date, Gavi has maintained its future financial commitment to supporting TCV introductions. Thus, the age of TCVs is finally dawning, and the global health community is poised with a unique opportunity to make significant impact.

CALL FOR ACTION

We are now sitting at a critical inflection point for typhoid fever control and prevention. The new data from Africa contained in this supplement give further evidence to the need to move swiftly toward interventions to address this problem. While we know that broad economic development, sustained improvements in water and sanitation, and strengthened health systems and food safety policies will go a long way toward reducing the burden of typhoid, we cannot afford to wait for the time it will take for these structural improvements to come along. We know that vaccines can and will have a significant impact on mortality and morbidity reduction, and we cannot let the story of TCVs unfold in the same way as the previous typhoid vaccines have done. The time to act is now to create the coordinated momentum needed to ensure that new data on disease burden translate into targeted action to make interventions widely available for those who need them the most.

Notes

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