Typhoid fever control in the 21st century: where are we now?

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Purpose of review
Momentum for achieving widespread control of typhoid fever has been growing over the past decade. Typhoid conjugate vaccines represent a potentially effective tool to reduce the burden of disease in the foreseeable future and new data have recently emerged to better frame their use-case.

Recent findings
We describe how antibiotic resistance continues to pose a major challenge in the treatment of typhoid fever, as exemplified by the emergence of azithromycin resistance and the spread of *Salmonella* Typhi strains resistant to third-generation cephalosporins. We review efficacy and effectiveness data for TCVs, which have been shown to have high-level efficacy (≥80%) against typhoid fever in diverse field settings. Data from randomized controlled trials and observational studies of TCVs are reviewed herein. Finally, we review data from multicountry blood culture surveillance studies that have provided granular insights into typhoid fever epidemiology. These data are becoming increasingly important as countries decide how best to introduce TCVs into routine immunization schedules and determine the optimal delivery strategy.

Summary
Continued advocacy is needed to address the ongoing challenge of typhoid fever to improve child health and tackle the rising challenge of antimicrobial resistance.

Keywords
antimicrobial resistance, typhoid fever, vaccines

INTRODUCTION

Typhoid fever remains a major public health challenge in low-resource settings. The nature of this challenge is highlighted by the persistent high-level morbidity and mortality across several regions, coupled with emergence of extensively drug-resistant (XDR) isolates of *Salmonella enterica* subspecies *enterica* serovar Typhi (*S.* Typhi). In many settings, treatment options are now severely limited, validating its status as a priority pathogen for antimicrobial resistance research.

Fortunately, the development, testing, and rollout of highly effective typhoid conjugate vaccines (TCVs) offer one effective tool to achieve meaningful disease control in the foreseeable future. In this review, we will highlight new research developments in typhoid fever epidemiology, diagnosis, treatment, and prevention since the publication of our previous review [1]. We will provide an overview of areas of ongoing study and identify knowledge gaps that need to be addressed to ensure that the global health community consolidates the gains made over the past decade.

BURDEN OF DISEASE

The past decade has seeen marked refinements in estimates of typhoid fever incidence, including from systematic reviews, modelled estimates, and population surveillance studies [2–4,5▪▪,6▪▪]. Most of these studies have demonstrated a trend towards declining global incidence over the past 20 years, albeit with sustained high rates of disease in several regions.

Investigators from the Institute for Health Metrics and Evaluation have updated modelled

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KEY POINTS

- Typhoid fever remains a major public health challenge in low-resource settings, and several recent surveillance studies have allowed for refined estimates of disease burden.
- The emergence of azithromycin-resistant and ESBL-producing strains of *Salmonella* Typhi presents a challenge to effective treatment.
- Typhoid conjugate vaccines (TCV) have demonstrated high-level efficacy and effectiveness in diverse field settings.
- Typhoid conjugate vaccines are being programmatically deployed in high-burden settings and offer the potential to reduce morbidity, mortality, and antimicrobial resistance.

estimates for *S*. Typhi, indicating that it was responsible for 9.24 million cases [95% confidence interval (CI) 5.94–14.13], 8.05 million (3.86–13.93) disability-adjusted life years (DALYs), and 110 029 (95% CI 52 810–191 205) deaths in 2019. This is compared with an estimated more than 20 million annual cases in 1990 [3]. The highest burden of disease is estimated to be in children 5–9 years of age, followed by 10–14-year-olds and 1–4-year-olds.

Several multicountry, standardized, population-based blood culture surveillance studies have improved our overall understanding of typhoid fever incidence [4,5▪▪,6▪▪]. The Surveillance for Enteric fever in Asia Project (SEAP) was a prospective blood culture surveillance study conducted at five hospitals in Bangladesh, Nepal, and Pakistan [6▪▪]. They employed a hybrid surveillance model, combining hospital-based blood culture surveillance and healthcare-utilization surveys, to estimate the burden of disease. High rates of disease were observed at all sites. After adjusting for blood culture sensitivity, probability of consent and blood sampling, probability of care-seeking at a study facility, and wealth and education multipliers, the authors presented adjusted estimated incidence of typhoid fever (adjusted) was as high as 1110 per 100 000 person-years in Dhaka, Bangladesh; 330 per 100 000 person years in Kathmandu, Nepal; 271 per 100 000 person years in Kavrepalanchok, Nepal, and 126–195 per 100 000 person years in Karachi, Pakistan.

The Strategic Typhoid Alliance across Africa and Asia (STRATAA) study employed multicomponent passive febrile illness surveillance study in three densely populated urban sites in Bangladesh, Nepal, and Malawi [5▪▪]. After adjusting for blood culture sensitivity, probability of receiving a blood culture and health-seeking behaviour, the authors presented adjusted estimates for typhoid fever of 1062 cases per 100 000 person-years of observation in Kathmandu, Nepal; 1135 cases per 100 000 person-years in Dhaka, Bangladesh and 444 cases per 100 000 person-years in Blantyre, Malawi. Burden of disease estimates were even higher when defined using serological surveillance.

Collectively, all studies to date have consistently demonstrated a high burden of typhoid fever in South and South-East Asia. New data suggested higher than previously thought incidence rates in parts of sub-Saharan Africa [5▪▪,7], which will be further refined by data from the upcoming Severe Typhoid Fever in Africa (SETA) study [4]. Accurate estimates of disease burden are becoming increasingly important given the advent of new control strategies such as TCVs, as countries decide how best to introduce TCVs into routine immunization schedules and determine the optimal delivery strategy.

IMPROVED DIAGNOSTICS FOR SURVEILLANCE

There is an ongoing need to develop and validate rapid, low-cost diagnostics for surveillance of typhoid fever. The current *de facto* gold-standard remains blood culture, which is routinely used in clinical practice (wherever available) and is recommended for routine surveillance of typhoid fever by the WHO. Blood culture diagnostics have several limitations, including: prolonged time-to-result; moderate sensitivity (40–60%, depending on prior antibiotic consumption and volume of blood drawn [8]), and the need for significant training and a consistent supply chain [9]. Novel, rapid diagnostics could facilitate appropriate antimicrobial prescribing practices as well as to improve local, regional, and global estimates of disease burden.

New approaches to serological surveillance using novel serological markers of infection and/or carriage (such as HlyE and CdtB) are being validated in multiple sites where blood culture surveillance is also ongoing and appear promising [10▪▪,11]. Approaches to validating standardized methods for detection of *S*. Typhi in environmental samples are also under evaluation in Blantyre, Malawi, and Vellore, India [12]. In the future, these approaches could potentially help fill regional data gaps, inform decision-making around TCV introduction, and could also be expanded to include surveillance of other epidemiologically relevant pathogens.

TREATMENT

Extended-spectrum cephalosporins are an important treatment option for enteric fever, particularly following the emergence of multidrug resistance (MDR) and fluoroquinolone resistance [13,14]. Since 2016, an outbreak of XDR *S.* Typhi has been identified in Pakistan, caused by an H58 clade harbouring MDR resistance, fluoroquinolone resistance, and extended-spectrum cephalosporin resistance, acquired through a plasmid encoding the $bla_{\text{CTX-M-15}}$ gene [15]. Over 15 000 XDR cases have been reported from Pakistan since then, with spread from the Sindh province to other areas in Pakistan [16]. Although XDR *S.* Typhi is not currently endemic in other countries, multiple countries have reported imported cases in travellers returning from Pakistan, highlighting the risk of further spread [17–25].

Third-generation cephalosporin resistance in *S.* Typhi isolates distinct from the XDR strain have also been reported. Case reports of *S.* Typhi encoding extended spectrum beta lactamase (ESBL) $bla_{\text{CTX-M-15}}$ have been reported from Democratic Republic of Congo and in travellers from Iraq [26,27]. Multiple reports from India describe ESBL isolates that carry plasmids, which encode $bla_{\text{SHV-12}}$, $bla_{\text{CMY-2}}$, $bla_{\text{ACC-1}}$, and $bla_{\text{DHA-1}}$ mutations [28▪]. Although cephalosporin resistance is not currently widespread (<5% of global strains), cases are increasing. The emergence of new, independent, mutations is concerning. The emergence of XDR *S.* Typhi can be considered an inflection point in typhoid fever control, providing an impetus to roll out TCVs more broadly to address the challenge of antimicrobial resistance [29▪▪,30].

Azithromycin is now the suggested treatment option for uncomplicated XDR or ESBL *S.* Typhi in endemic and nonendemic settings [31,32]. The emergence of azithromycin resistance is a major cause for concern. Resistant isolates have been reported in multiple settings, including Bangladesh [33], Pakistan [34], Nepal [35], India [36▪], Singapore [37], and Samoa [38]. Resistance is largely mediated by a point mutation in the *acrB* gene, which codes for an efflux pump. These mutations have appeared independently in multiple genetically distinct lineages and appear to be concentrated in areas with significant antimicrobial selection pressure where azithromycin is increasingly used as first-line treatment for typhoid and other blood stream infections. Programmatic distribution of azithromycin in some areas of the world, for example, mass administration for trachoma prevention and elimination, may further contribute to this, highlighting the need for ongoing genomic surveillance and monitoring in these settings and more broadly.

Carbapenems are now increasingly used to treat drug-resistant enteric fever. There are no randomized controlled trials evaluating the use of meropenem in enteric fever; however, observational data suggest it is effective as a treatment [39]. The use of carbapenems is limited by cost and the need to give them intravenously. Newer oral carbapenems such as tebipenem may be an effective option in the future, but further clinical trials are needed [40].

CARRIAGE

Chronic gallbladder carriage of *S.* Typhi remains poorly understood. Genomic studies of gallbladder isolates show that carriage isolates have comparable genotype distributions to circulating blood culture isolates in the same setting – including MDR strains [41▪,42]. Carriage isolates appear to have higher rates of mutations in membrane lipoproteins, transport proteins, surface antigens, and genes involved in polysaccharide synthesis [41▪,42]. A recent 3-year case–control study in an informal settlement of Nairobi, Kenya estimated a chronic carriage rate of 1.1% in children aged 16 years or less, highlighting a role for paediatric carriage in onward transmission in this setting [42]. There is limited available data to suggest treatment options for chronic carriage in an era of high fluroquinolone resistance [43]. A 28-day course of azithromycin can be used to treat fluoroquinolone-resistant carriers, although there is no trial evidence to assess this. Understanding how to diagnose and treat enteric fever chronic carriers remains a neglected area of research.

THE ERA OF TYHPOID CONJUGATE VACCINES

In 2017, SAGE issued updated policy recommendation for the use of typhoid vaccines in endemic countries. For the first time, this included a recommendation for programmatic use of TCVs in children aged under 2 years [44]. The SAGE recommendation was based primarily on safety and immunogenicity data [45,46▪], supported by evidence of efficacy in human challenge studies conducted in healthy adults [47], in the context of efficacy data from earlier generation TCVs [48]. The most studied TCV is a Vi polysaccharide-tetanus toxoid (Vi-TT) conjugate vaccine Typbar-TCV, manufactured by Bharat Biotech (Hyderabad, India). Typbar-TCV has been shown to be well tolerated and immunogenic on children as young as 6 months of age [46▪] and was prequalified in December 2017. TYPHIVEV – a Vi-CRM_{197} conjugate manufactured by Biological E (Pune, India) – has a comparable safety and immunogenicity profile to Typbar TCV [49] and received prequalification in December 2020.

Pivotal efficacy and effectiveness data for Typbar-TCV were generated by the Typhoid Vaccine Acceleration Consortium (TyVAC), led by the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH. The TyVAC consortium evaluated Typbar-TCV in three large postlicensure efficacy and effectiveness studies – individually randomized trials in Malawi [50▪▪] and Nepal [51], alongside a cluster-randomized trial in Bangladesh [52▪▪]. Each trial had a unique design, but point estimates for efficacy against culture-confirmed typhoid fever were approximately 80% at 18–24 months in all study sites. High-level results are detailed in Table 1.

Previous studies have demonstrated some evidence for indirect protection conferred by Vi-polysaccharide vaccines [53]. The TyVAC investigators assessed whether Typbar-TCV conferred indirect protection in the Bangladesh cluster randomized trial [52▪▪]. They compared the incidence of typhoid fever among unvaccinated persons in Typbar-TCV clusters compared with unvaccinated persons in Japanese Encephalitis vaccine clusters. In this study, there was no evidence of significant indirect protection conferred by the typhoid conjugate vaccine. The authors noted that the study was not adequately powered to assess the anticipated level of herd protection (20%), and any indirect protection may have been diluted in the densely populated clusters. A cluster randomized trial of Typbar-TCV is currently underway in Asante-Akim, Ghana, which is anticipated to generate additional data on indirect protection in a different epidemiological context [54].

Several observational studies have since reinforced data on the effectiveness of TCVs (Table 1) [29▪▪,30,55,56]. The Navi Mumbai Municipal Corporation (NMMC) conducted the first public-sector TCV campaign with Typbar-TCV in 2018.[55] Vaccine effectiveness was estimated using a case–control design among age-eligible residents in urban health centres with typhoid fever, and age-matched and time-matched controls were randomly selected from a population-based household survey. Seven (17%) cases and 86 (51%) controls reported having received TCV, yielding an adjusted odds ratio of 0.184 (95% CI 0.074–0.46; $P = 0.0003$), equivalent to an effectiveness estimate of 81.6% (95% CI 54–92.6%).

Following an outbreak of XDR *S.* Typhi in Hyderabad, Pakistan, a reactive vaccination campaign using Typbar-TCV was conducted from February to December 2018, covering 207 000 children 6 months to 10 years of age [29▪▪]. A household census was conducted at baseline and active blood culture surveillance was established in hospitals, clinics, and laboratories. The vaccine effectiveness analysis included 24 407 children from the census registry and surveillance system, 13 436 of whom had received TCV. In this cohort study, Typbar-TCV was 55% effective (95% CI 52–57) against suspected typhoid fever, 95% (93–96%) effective against blood culture-confirmed typhoid fever and 97% (95–98%) effective against XDR *S.* Typhi in 6-month-olds to 10-year-olds.

A mass vaccination campaign using Typbar-TCV was also conducted in Lyari Town (an urban slum neighbourhood of Karachi, Pakistan) in response to the spread of XDR typhoid to this area. Effectiveness was evaluated using a matched case–control design [30]. Surveillance was conducted at three hospitals from August to December 2019, and children aged 6 months to 15 years presenting to a study facility with blood culture-confirmed *S.* Typhi were counted as cases. For each case, at least one age-matched afebrile facility control and two age-matched afebrile community controls were enrolled. Of the 82 confirmed typhoid cases, 8 (9.8%) had received TCV. Among the 163 community controls and 82 facility controls, 23.2 and 32.9% had received TCV, respectively. The age-adjusted and sex-adjusted TCV effectiveness was 72% (95% CI 34–88%).

Immunogenicity data for TCVs appear promising. A single dose of Typbar-TCV induces durable anti-Vi IgG above baseline out to 5 years [46▪]. The significance of anti-Vi IgG in conferring protection is yet to be determined, and work is ongoing to better define correlates of protection. The immunogenicity of Typbar-TCV is comparable across all study sites where efficacy has been demonstrated, although results may vary by local epidemiology owing to natural boosting. TyVAC investigators also conducted immunogenicity and co-administration studies in infants and toddlers in Burkina Faso. The available data have shown no evidence of TCV interference with multiple EPI vaccines, across diverse settings [57,58].

There is currently a comparatively robust TCV development pipeline. Four companies have programmes with a TCV candidate with phase III clinical trials ongoing or completed – BioTCV [Vi polysaccharide conjugated to diphtheria toxoid (Vi-DT), PT Biofarma, Indonesia], EuTYPH-C (Vi-CRM197, EuBiologics, South Korea) [59], SKYTyphoid (Vi-DT, SK Bioscience, South Korea) [60], and ZYVAC TCV (Vi-TT, Zydus Cadila, India, licensed in India). All four manufacturers are seeking WHO prequalification. This bodes well for future supply security as part of a healthy market framework. Licensure and prequalification of these vaccines will likely be based on safety and immunogenicity data that demonstrate noninferiority compared with Typbar-TCV. Additional

Table 1. overview of efficacy and effectiveness data for Typbar-TCV

Study site	Design	Control vaccine/ control group	Age	Number vaccinated	Duration follow-up	Vaccine efficacy or effectiveness (95% CI)[a]	Reference
Lalitpur, Nepal	Individually randomized	Meningococcal capsular group A conjugate vaccine	9 months to 16 years	20 019	24 months	79.1% (62.0–88.5)	[61]
Blantyre, Malawi	Individually randomized	Meningococcal capsular group A conjugate vaccine	9 months to 12 years	28 130	18–24 months	83.7% (68.1–91.6)	[50▪▪]
Dhaka, Bangladesh	Cluster randomized	SA 14–14-2 Japanese encephalitis (JE) vaccine	9 months to 16 years	67 395	24 months	85% (76.0–91.0)	[52▪▪]
Observational studies							
Navi Mumbai, India	Case–control (routine immunization)	Community controls	9 months to 14 years	160 000	15 months	80.2% (53.2–91.6)	[55]
Karachi, Pakistan	Case–control (outbreak response campaign)	Facility and community controls	6 months to 15 years	87 993	4 months	72% (34–88)	[30]
Hyderabad, Pakistan	Cohort study (outbreak response campaign)	Community controls	6 months to 10 years	207 000	18 months	95% (93–96)	[29▪▪]
Harare, Zimbabwe	Case–control (outbreak response)	Community controls Facility controls	6 months to 15 years	320 000	18 months	75% (1–94) 84% (57–94)[b]	[56]

[a]Blood culture-confirmed typhoid fever.
[b]Efficacy in 6 months to 45 year cohort compared with community controls was 67% (95% CI 33–83) Bangladesh [52▪▪] and individually-randomized trials in Malawi [50▪▪] and Nepal [51].

studies demonstrating efficacy or effectiveness against clinical disease may have an impact on country product preferences.

TCVs have been introduced into routine childhood immunization programmes in six countries to date. The first public sector TCV introduction was conducted at a subnational level in India in the Navi Mumbai Municipal Corporation and included an effectiveness and safety evaluation (Table 1). Pakistan was the first country to initiate a Gavi-supported national introduction in 2019, followed by Liberia (2021), Zimbabwe (2021), and Nepal (2022). Malawi also plans to introduce TCV with Gavi support in 2022. The Samoan government initiated a self-financed TCV introduction in 2021.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Additional data are expected in the next 12–18 months that will help to inform TCV-deployment decisions. It is important to understand the duration of protection conferred by a single dose of a TCV and whether a booster dose is needed. As the TCV pipeline expands, it will be important to establish whether different TCV products can be used interchangeably as part of a primary dose with booster regimen, as countries may switch TCV products because of supply limitations, vaccine price, or availability of new data. Laying the groundwork to interrogate these questions now would seem logical rather than waiting until the need for a booster dose is definitively established, as setting up and conducting interchangeability studies will take time. Additionally, further studies are required to assess if efficacy varies depending on the initial age of administration and the background burden of disease, which may impact natural boosting.

Identification of a correlate of protection [62] could accelerate testing and postlicensure assessments of newer vaccines, which could create

additional demand for newer TCVs, but this may not be feasible in the short-term.

Understanding the impact of TCVs on AMR is also an important research need. There are several ways to potentially assess this – through measurements focused on pathogens in people (e.g. measuring the impact of TCV on incidence of infections caused by drug-resistant *S*. Typhi), or on antimicrobials (e.g. measuring the impact of TCV on antimicrobial consumption or use), or the environment [e.g. measuring impact of TCV introduction on prevalence of antimicrobial resistance genes (ARGs) in pooled environmental samples]. With the increasing prevalence and severity of AMR in circulating *S*. Typhi, particularly in South Asia, establishing the impact of TCV on AMR will be important in demonstrating the full public health value of TCVs, and guidance to countries for how best to measure this would be valuable.

CONCLUSION

In our previous review, we noted that several opportunities for achieving control of typhoid have been missed in the past [1]. The global health community is entering a new stage where we have high-level efficacy data for TCVs and a robust pipeline in development, allied with financial and regulatory support. Nevertheless, TCVs have been adopted in only small number of countries to date, and uptake has arguably been slower than anticipated in both Gavi and non-Gavi countries – driven in part by limited evidence of typhoid disease and economic burden in some countries, the COVID-19 pandemic, and other competing priorities. There is little room for complacency, and continued advocacy is needed to address the ongoing challenge of typhoid fever to improve child health and tackle the rising challenge of antimicrobial resistance.

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