

A Vaccine Is a Bridge

The New Era of Typhoid Prevention



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Introduction

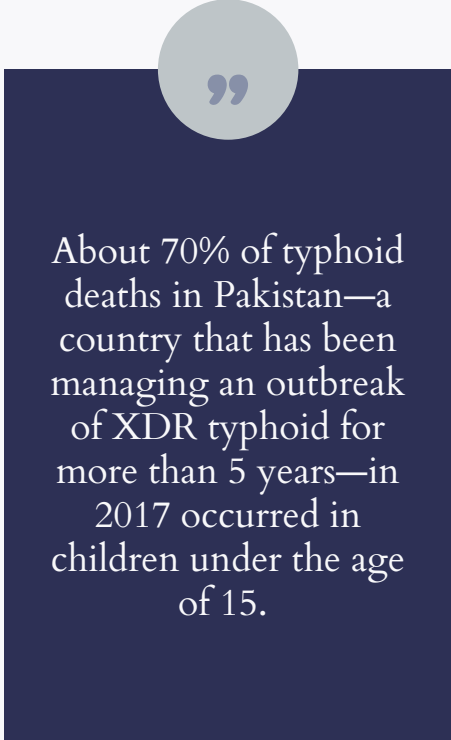
Salmonella enterica serovar Typhi, the bacterium that causes typhoid, is steadily growing more resistant to antibiotic treatment and, in some cases, has become multidrug-resistant (MDR) or extensively drug-resistant (XDR). Humans are typhoid's only known reservoir, and typhoid fever predominantly affects children in areas where the bacteria is endemic or causes frequent outbreaks. In recent years, much attention has been paid to the development of typhoid conjugate vaccines (TCVs), which represent a significant improvement over older typhoid vaccines and have proven to spur longer-lasting immunity in children. As of this writing, the World Health Organization (WHO) has prequalified two TCVs, in 2017 and in 2020. TCV introduction into the national immunization schedules of four countries—Liberia, Nepal, Pakistan, and Zimbabwe—largely occurred during the COVID-19 pandemic.

In this CIDRAP-ASP report, we examine what is known about the global burden and drug resistance of typhoid; the use of TCVs during outbreaks and as part of new country-wide immunization campaigns during the COVID-19 pandemic; the importance of public health interventions that address an array of health, socioeconomic, cultural, and economic factors rather than relying solely on vaccines; and the urgency of including community-based needs and solutions in global, national, and local discussions about antibiotic resistance.

The Global Burden of Typhoid and the Impact of Drug Resistance

Symptoms of typhoid include fever, abdominal pain, malaise, headache, diarrhea or constipation, and sometimes a rash or cough. Typhoidal *Salmonella* leads to infection when someone consumes contaminated food or water, and outbreaks often are associated with rainy seasons in areas that lack sanitation infrastructure. If left untreated, the infection can cause febrile delirium, intestinal hemorrhage and perforation, dehydration, malnutrition, and death.

WHO data from 2018 assert that 21 million cases of typhoid, 222,000 of which are fatal, occur annually around the world, though because of a dearth of standardized data collection across endemic regions, this number is thought to be grossly underestimated (CDDEP 2021). People who recover and/or receive antibiotic treatment may still become carriers of the bacteria and transmit it to others in situations where sanitation is poor or non-existent. Because signs and symptoms mimic many other febrile conditions, diagnosis is difficult, especially in regions that lack laboratory testing facilities.



“About 70% of typhoid deaths in Pakistan—a country that has been managing an outbreak of XDR typhoid for more than 5 years—in 2017 occurred in children under the age of 15.

Children bear the brunt of the global typhoid burden, particularly across endemic regions of South and Southeast Asia and sub-Saharan Africa. Data from India show that typhoid and paratyphoid fever caused almost 20% of all deaths among children ages 5 to 14 in 2016 (CDDEP 2021). About 70% of typhoid deaths in Pakistan—a country that has been managing an outbreak of XDR typhoid for more than 5 years—in 2017 occurred in children under the age of 15 (Gavi 2020). Compounding children’s susceptibility to severe illness and death from typhoid complications or lack of treatment has been the fact that available typhoid vaccines failed to provide long-lasting immunity in younger people. Immunization is only one piece of typhoid control efforts,

however, as access to clean water is essential for prevention of both typhoid cases and transmission of drug-resistant strains. The first report on global prevalence of potable water availability and sanitation services was published in 2017, bringing to light the fact that 2.1 billion people do not have access to clean water at home, while 4.5 billion live without sanitation services (UNICEF and WHO 2017).

MDR and fluoroquinolone non-susceptible strains of typhoid may make antibiotic treatment difficult or impossible. Though Pakistan has garnered significant attention for an outbreak of XDR typhoid that has been ongoing since 2016, typhoidal *Salmonella* strains resistant to azithromycin have recently emerged in Bangladesh, India, Nepal, Pakistan, and Singapore. The proportion of fluoroquinolone non-susceptible strains has also been rising globally, with large increases observed in Bangladesh, India, Nepal, and Pakistan (Birger et al 2022, da Silva et al 2022).

Currently, no standardized treatment guidelines for typhoid exist, and antibiotics used to treat the infection include ciprofloxacin and chloramphenicol (for non-pregnant people), ceftriaxone, ampicillin, and sulfamethoxazole/trimethoprim (CDDEP 2021). Three antibiotic therapies—azithromycin, carbapenems, and tigecycline—can effectively treat XDR typhoid, of which azithromycin is the only oral option that can be given in outpatient settings (Butt et al 2022).

The Introduction of Typhoid Conjugate Vaccines (TCVs)

TCVs, introduced for use only within the past decade, represent a new paradigm in typhoid immunization. TCVs induce a T-cell–dependent immune response and are more likely to spur strong, long-term immunity in children than the oral Ty21a vaccines and parenteral Vi polysaccharide vaccines recommended in 2008 by the WHO for typhoid prevention in endemic regions (Shakya et al 2021).

As of 2022, the WHO has prequalified two TCVs, meaning that each vaccine meets international standards for safety and efficacy and can be procured by United Nations agencies (WHO 2018). Both prequalified vaccines are produced in India and have demonstrated similar safety and immunogenicity. In Typbar TCV, prequalified in 2017, the Vi polysaccharide outer capsule of *Salmonella enterica* serovar Typhi is conjugated to a tetanus toxoid carrier protein (Qadri et al 2021). Typhibev TCV, prequalified in 2020, conjugates a Vi polysaccharide from *Citrobacter freundii* sensu lato to a CRM197 carrier protein; CRM197 is a non-toxic diphtheria toxin mutant (Shakya et al 2021, WHO 2021a).

TCV Immunization Campaigns

Typhoid conjugate vaccine (TCV) immunization campaigns typically include a combination of approaches, including:



Inclusion of TCV in immunization recommendations for infants



Catch-up campaigns to vaccinate older children in communities and schools




Geographically focused initiatives to assure access in rural areas, address an increase in cases during the rainy season, or help to stem an outbreak

Four countries have introduced TCVs into their national immunization schedules as of the time of this writing: Pakistan in 2019, Liberia and Zimbabwe in 2021, and Nepal in 2022. Complicating the rollout of TCV, however, is the relative dearth of surveillance data on typhoid burden and antibiotic susceptibilities, with many endemic regions lacking the ability to confirm cases with blood culture or expand surveillance programs to remote areas (Shakya et al 2021).


In May 2020, the WHO began tracking delays in vaccine-preventable disease immunizations as a result of the COVID-19 pandemic, and though several TCV campaigns had to be postponed during 2020 and early 2021, TCV immunization was the only vaccine initiative that had caught up on postponements and had no canceled campaigns as of December 2021 (Ho et al 2022).

National Typhoid Conjugate Vaccine (TCV) Immunization Campaigns: 2019–2022



Pakistan is the first country to have included TCV in its national immunization program and began large-scale vaccination campaigns in 2019 in Sindh province, a region that has been facing an outbreak of XDR typhoid since 2016.

XDR typhoid in Pakistan is resistant to ampicillin, chloramphenicol, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins.



Liberia, in early 2021, was the first country in sub-Saharan Africa to introduce TCV into the routine immunization schedule, drawing on assistance from Gavi and the PATH Typhoid Vaccine Acceleration Consortium.

Liberia’s process involved developing roadmaps for TCV introduction, holding training workshops, creating a robust communications campaign, and planning for ways to reach rural and isolated communities.



Zimbabwe added TCV to its routine immunization program in 2021, after extensive vaccination campaigns. An outbreak of ciprofloxacin-resistant typhoid from October 2017 to February 2018 spurred a 2019 immunization campaign that resulted in more than 300,000 doses of TCV administered to children between 6 months and 15 years in and around Harare.

In May 2021, Zimbabwe initiated a 10-day typhoid vaccination campaign for children between 9 months and 15 years, which vaccinated more than 4 million children by September 2021. The campaign ended with Zimbabwe’s Expanded Programme on Immunization introducing TCV given with the first dose of measles vaccine to 9-month-old babies.

Both the 10-day mass vaccination campaign and the integration of TCV into the routine childhood immunization schedule occurred during the COVID-19 pandemic, and planning for both was interrupted several times and adapted to ensure compliance with social distancing guidelines.



Nepal introduced TCV into the national immunization program in early 2022. A campaign that provided TCV to children between the ages of 15 months and 15 years at more than 50,000 locations around the country served as a prelude to the formal introduction of TCV into the vaccination schedule for 15-month-old children.

The immunization campaign also aimed to offer missed childhood vaccines—such as diphtheria, tetanus, and pertussis vaccines—to infants between 15 and 23 months old.

Sources: Butt M.H., A. Saleem, S.O. Javed, et al. 2022. “Rising XDR-Typhoid Fever Cases in Pakistan: Are We Heading Back to the Pre-antibiotic Era?” *Frontiers in Public Health*. Gavi. 2020. “Typhoid: immunising against antimicrobial resistance.” Gavi. 2022. “Nepal introduces Typhoid vaccine into routine immunisation across the country.” Butt M.H., A. Saleem, S.O. Javed, et al. 2022. “Rising XDR-Typhoid Fever Cases in Pakistan: Are We Heading Back to the Pre-antibiotic Era?” *Frontiers in Public Health*. Oberman E. 2021. “Typhoid conjugate vaccine arrives in Zimbabwe.” *Coalition Against Typhoid*. World Health Organization. 2021. “Liberia becomes the first country in sub-Saharan Africa to introduce Typhoid Conjugate Vaccine (TCV): Over 1 million children to be reached.” World Health Organization. 2021. “Stories from the field: How vaccines can help to prevent antibiotic resistance—Zimbabwe’s response to drug-resistant outbreaks of typhoid and cholera.” Dapaah P. and J. Farley. 2020. “The long bumpy road to typhoid conjugate vaccine introduction.” *PATH*.

The Implications and Future of TCVs

TCVs in Development

While significant focus has been on Typbar TCV and Typhibev TCV as the vaccines are introduced into national immunization campaigns or used to quell outbreaks of enteric fever, other TCVs are in various stages of development and licensure. These include: PedaTyph, which is licensed for use in India but has not received WHO prequalification; ZyVAC TCV, which is licensed in India and has demonstrated non-inferiority to the prequalified Typbar TCV; Vi-DT, which is awaiting results from phase 3 clinical trials (Shakya et al 2021), and EuTCV, which has recently begun phase 3 clinical trials (Ndiaye and Cisse 2022).

Health and Economic Implications

A study modeling the effect of TCV campaigns across 73 lower-income countries found that routine vaccination for 9-month-old children combined with a catch-up campaign for children up to 15 years would avert 66.7 million typhoid fever cases over 10 years. Averted cases would include 42.5 million cases and 506,000 deaths caused by fluoroquinolone-nonsusceptible typhoid and 21.2 million cases and 342,000 deaths caused by MDR typhoid, with significant benefit likely to occur in India, Nigeria, and Pakistan. Interestingly, the models found that TCV immunization on a grand scale had a greater effect on averting cases and deaths attributed to drug-resistant typhoid compared with antibiotic-sensitive typhoid (Birger et al 2021).

Few studies have examined cost-effectiveness of mass TCV vaccination campaigns or of introducing the vaccine into a national immunization schedule. Cost-effectiveness varies significantly by country, depending on national immunization budget (including the proportions of the budget that are domestically versus internationally sourced), proportion of urban to

rural population and access to healthcare services in rural areas, the presence of people who may carry typhoid chronically and unknowingly transmit the disease, current typhoid incidence, population acceptance of typhoid vaccine, the presence and state of sanitation services and clean drinking water, and country-specific vaccine costs negotiated with the manufacturers (CDDEP 2021).


A model of TCV introduction in India found that routine vaccination combined with community availability of TCV for children ages 1 to 15 years could avert about 30 million cases of typhoid and save \$1.6 billion to \$2.2 billion USD over 10 years if introduced across urban and rural areas. Initial costs incurred during the first year of routine vaccination would range from \$21 million to \$56 million, while catch-up campaigns that covered a significant swathe of the country would cost about \$794 million to \$928 million, an effort that would significantly challenge India's 2017–2018 immunization budget of about \$1.1 billion USD. The researchers note that more than 70% of the costs associated with typhoid in India are not healthcare-related and are largely associated with lost wages from missing work to care for children, family members, or self (Ryckman et al 2021).

Malawi has also been considering the cost-effectiveness of introducing TCV into the country's immunization program and applied for funding from Gavi in 2020. Vaccines, immunization supplies and services, training programs, and communications campaigns will likely cost Malawi about \$8.5 million USD over 3 years, while total economic costs will be near \$29.8 million USD. A significant amount of start-up operational costs may be offset by Gavi contributions (Debullet et al 2022).

Typhoid Control and a Vaccine-Inclusive Public Health Response

While the availability of TCV represents a major stride toward preventing childhood mortality in much of the world, the vaccine must be viewed as a bridge to a structural solution to typhoid elimination and not as a solution in and of itself.

Because the bacterium has no known animal reservoir, global typhoid elimination is biologically possible. The societal drivers of typhoid incidence, outbreaks, and drug resistance, however, are vast and include the availability of clean water and sanitation, access to clinical guidelines and affordable diagnostics for febrile illnesses, food safety, maternal health and the ability or choice to breastfeed, religious and cultural objections to vaccination, the ability of some people to chronically carry and transmit the disease even following treatment, and the pervasive vestiges of colonialism (Stanaway et al 2020, Dolecek 2020).



The use of azithromycin as a COVID-19 therapy may reduce the effectiveness of the last remaining oral option for treating XDR typhoid, a burden that would fall primarily on poor communities that may not be able to access or afford hospital-based care.

Researchers and clinicians with experience introducing TCV in Pakistan have argued for a broad approach to typhoid control that is not entirely dependent on vaccines. In August 2021, Pakistan reported 52 new cases of XDR typhoid, spurring concerns that rises in new cases and increased transmission, especially in poorer areas of cities, could lead to severe outbreaks and overwhelm the health system during the pandemic. Though poor sanitation and inappropriate antibiotic use are known contributors to drug-resistant typhoid, XDR typhoid causes and control mechanisms must also be considered within the context of a healthcare and public health system focused on managing COVID-19.

Problems that likely have contributed to the rise in XDR typhoid in Pakistan include the use of contaminated water for drinking or irrigation, the detrimental effect of COVID-19 on typhoid control programs and healthcare availability, poor diagnostic methods that lead to indiscriminate empirical antibiotic use, population increases and crowding in cities such as Karachi, a growth in urban slums where access to clean water and healthcare is limited, and religious or cultural objections to widespread immunization programs.

The use of azithromycin as a COVID-19 therapy may reduce the effectiveness of the last remaining oral option for treating XDR typhoid, a burden that would fall primarily on poor communities that may not be able to access or afford hospital-based care. For typhoid management to be sustainable and prevent future outbreaks, especially in situations of prevalent XDR and MDR cases, it should involve improvements to sanitation and access to clean drinking water, significant infrastructure investment in poor areas, increased public awareness of hygiene and preventive measures, and regulations to prevent antibiotic overprescribing (Butt et al 2022).

A recent report from the WHO and UNICEF found that only 16% of healthcare facilities in Pakistan and 17% of healthcare facilities in Zimbabwe had basic sanitation services; data were unavailable for Liberia and Nepal (WHO 2022). While the improvement of water, sanitation, and hygiene (WASH) programs represent an integral step toward preventing typhoid incidence and transmission, a greater emphasis on maternal health and food safety is also necessary for a robust and sustainable typhoid prevention program. Breastfeeding programs may ensure that fewer infants are exposed to contaminated food and water (CDDEP 2021).

Food safety and other interventions that prevent diarrheal illness and malnutrition in children play a significant role in averting deaths from typhoid. Food- and nutrient-based public health interventions are often not integrated into infectious diseases programs and are subject to numerous problems associated with global supply chains, the availability of nutritional supplements such as zinc and electrolytes to treat diarrhea and prevent dehydration, and the fact that young children not in school may not have a reliable source for a midday meal (CDDEP 2021).

In an examination of the history of typhoid and its effects on outbreaks and the emergence of drug-resistant strains, Claas Kirchhelle, DPhil, MA, and Samantha Vanderslott, MSc, describe how the elimination of typhoid in high-income countries was accompanied by a public health response that treated typhoid as something spread by travelers from low-income areas (Kirchhelle and Vanderslott 2019). Forgetting the investments in sanitation and food security that had accompanied typhoid's withdrawal from wealthier countries, many high-income nations began to view the disease as a problem that could be solved easily within their borders with vaccination and biosecurity. Typhoid, relegated to lower-income countries and thus deemed endemic, has long been viewed as a problem that mass vaccination can solve. Even with the introduction of effective TCVs that spur long-lasting immunity in children, however, typhoid can only be eliminated with the changes to sanitation and social infrastructure that heralded its demise as a major cause of child mortality in high-income nations.

Kirchhelle and Vanderslott say, “Whether we choose to justify action out of ethical considerations of collective responsibility or out of enlightened self-interest, the global threat posed by XDR typhoid and the conditions producing multiple resistant pathogens like it will only be overcome by more—and not less—international involvement.”

Recommendations and Next Steps

What does collective responsibility look like in an era of increasing TCV access amid the changes to traditional public health wrought by the COVID-19 pandemic? An emphasis on clean water, sanitation services, maternal health, and food safety and access are all integral, as is the political and economic will to invest in strategies that avert preventable deaths of children.

Not only are outbreaks of typhoid preventable, they are often predictable. The following actions may help to lay the groundwork for public health infrastructure in which the new TCVs have the opportunity to play a major part in ending typhoid.

1. Guarantee community access to antibiotics

Prioritize oral and largely community-prescribed antibiotics in global and national guidelines, as well as in all discussions about antibiotic access. Azithromycin is the last remaining oral antibiotic that is effective against XDR typhoid, yet a focus on preserving oral antibiotics that are commonly used in community settings often takes a back seat to preserving antibiotics that are used for healthcare-associated infections or infections often viewed as more complex. What cannot be overstated is that access to effective oral medicines *is* access to healthcare. Without access to effective oral antibiotic treatment, existing health inequities—especially those associated with geography, livelihood, and poverty—will become more prominent.

Empower community-led outbreak detection and data collection expertise. Tools and training for mobile community-led surveillance, especially in rural or slum areas, may also help flag the beginnings of outbreaks before they become more widespread.

2. Strengthen multilateral public health governance

At the national level, improve collaboration between programs working on antimicrobial resistance (AMR), infectious and zoonotic diseases, climate, water and sanitation, maternal and child health, and basic infection prevention and control.

Link the success of AMR and infectious diseases programs to investments in water, sanitation, and hygiene; maternal and child health; and basic infection prevention and control, especially when communicating with philanthropic organizations.

Ensure at the national level that new healthcare institutions—often considered beneficial political or philanthropic investments—are built with access to clean water, sanitation, and hygiene facilities.

3. Develop evidence-based typhoid guidelines

Given that the signs and symptoms of typhoid are nonspecific when compared with many childhood illnesses, a mix of technological (eg, rapid point-of-care diagnostic tests) and non-technological (eg, diagnostic algorithms and training for community clinicians and caretakers) may help link detection of typhoid to climate events, vaccination status, and socio-economic context.

The development of standardized global guidelines for typhoid treatment is sorely needed. Guidelines must emphasize the importance of preventing and appropriately treating diseases that occur in the community as a key strategy in managing AMR, advocate for the preservation of oral antibiotics, and be linked to programs that improve the ability to actually access care. Steps might include decentralized healthcare for those in rural areas and community health worker-led programs in slum areas of cities. Guidelines must also incorporate available and ever-changing evidence on AMR and make resistance-guided recommendations for the treatment of chronic typhoid carriers.

Conclusion

Four countries introduced a new and highly effective typhoid vaccine into their national immunization programs, largely during a pandemic that dealt massive blows to the national ability to carry out mass public health interventions. This extraordinary effort to prioritize the health and future of children should guide the global community's investments in ending typhoid and the myriad health and social inequities that contribute to its spread.

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Contact

Center for Infectious Disease Research
and Policy Antimicrobial Stewardship
Project (CIDRAP-ASP)

University of Minnesota
Minneapolis, Minnesota, USA

cidrap.umn.edu/asp
asp-cid@umn.edu
[@CIDRAP_ASP](https://twitter.com/CIDRAP_ASP)