Clinical Infectious Diseases

EDITORIAL COMMENTARY

Gateway to Typhoid Conjugate Vaccine Introduction in India and Beyond—Programmatic Effectiveness of a Public Sector Typhoid Conjugate Vaccine Campaign in Navi Mumbai

Megan E. Carey

Department of Infection Biology, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom

(See the Major Article by Hoffman et al. on pages 138–44.)

Keywords. typhoid conjugate vaccine; vaccine introduction; programmatic effectiveness; India.

Salmonella enterica serovar Typhi (*S.* Typhi) caused an estimated 9.24 million cases (5.94 M, 14.1 M) of typhoid fever in 2019, resulting in 110 000 deaths (52 800, 191 000) [1]. Over 4.8 million cases and 50 000 deaths are estimated to have occurred in India [1]. Increasing prevalence and severity of antimicrobial resistance (AMR) jeopardize effective typhoid fever control, particularly in South Asia, where resistance to all oral antimicrobials used to treat typhoid fever has been reported [2–6], and where disease incidence is highest. The advent of typhoid conjugate vaccines (TCVs), which promise to provide longer duration of protection than previously licensed typhoid vaccines and are suitable for use in children as young six months of age, represents a major opportunity to accelerate typhoid fever control and to slow the emergence and spread of AMR. The World Health Organization (WHO) recommends use of TCVs in routine immunization and catch-up campaigns for the prevention of typhoid fever in typhoid-endemic countries, particularly those where AMR *S.* Typhi is present [7]. Two TCVs have been prequalified by the WHO, with several additional vaccine candidates in late-stage clinical development, which bodes well for future vaccine supply security [8]. Five countries have introduced TCV into their national immunization programs (Pakistan, Liberia, Zimbabwe, Nepal, Samoa), and several additional countries are planning national introductions, yet a number of typhoid-endemic countries have not made the decision to introduce the vaccine.

A single dose of TCV has been shown to be safe, immunogenic, and highly efficacious (79%–85%) over 18–36 months in large randomized-controlled field efficacy trials conducted in Malawi, Nepal, and Bangladesh [9–14]. A single dose of TCV has been shown to be highly effective when delivered through vaccination campaigns in response to drug-resistant *S.* Typhi outbreaks in Pakistan and Zimbabwe [15–17]. In addition, TCV was highly effective (97%) against extensively drug resistant (XDR) *S.* Typhi in Pakistan [16]. There is enormous potential for TCVs to slow the emergence and spread of drug-resistant *S.* Typhi through the prevention of infections caused by drug-resistant strains, as well as reductions in antimicrobial use and decreased selection pressure [18].

In this issue of *Clinical Infectious Diseases*, Dr Seth Ari Sim-Son Hoffman and colleagues [19] share results from an effectiveness evaluation of a pediatric vaccination campaign using a WHO Prequalified TCV, Typbar-TCV® (Vi polysaccharide conjugated to tetanus toxoid, Bharat Biotech India Ltd., Hyderabad, India). This public sector campaign, which targeted children 9 months to 14 years of age, was conducted by the Navi Mumbai Municipal Corporation (NMMC) in Maharashtra, India in 2018. The campaign was intended to be biphasic, and a stepped wedge randomized controlled evaluation was planned [20], but the onset of the coronavirus disease 2019 (COVID-19) pandemic prevented the second stage of the campaign from occurring, leading investigators to evaluate the programmatic effectiveness of the initial campaign against community-level risk of typhoid fever using a test-negative design (TND).

Received 17 February 2023; editorial decision 01 March 2023; accepted 08 March 2023; published online 22 March 2023

Correspondence: M. E. Carey, Department of Infection Biology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT (megan.carey@lshtm.ac.uk).

Clinical Infectious Diseases® 2023;77(1):145–7

https://doi.org/10.1093/cid/ciad134

These are the first published effectiveness data from a non-outbreak response public sector mass vaccination campaign.

NMMC is divided into 22 urban health posts (UHPs) of roughly equal population size; investigators stratified these based on proportion of residents living in slum areas and randomly assigned equal numbers from each stratum to be included in the initial vaccination campaign or the second one. In total, 320 000 children were age-eligible for vaccination within NMMC, and 160 000 were targeted for the initial campaign, which achieved 71% coverage in the initial vaccination communities. Blood culture surveillance was established in 6 hospitals throughout NMMC, and a continuous community survey was planned to account for healthcare seeking behavior. The survey was halted on account of COVID-related risk to field workers, but blood culture surveillance continued throughout the duration of the 33-month study follow-up period (September 2018 to March 2021). Each *S.* Typhi blood culture positive case was matched with up to 3 blood culture negative febrile controls based on age and time of enrollment (±28 days). The adjusted odds ratio that a culture-confirmed typhoid case resided in a vaccination community was 0.44 (0.26, 0.75, $P = .0003$), meaning that the programmatic effectiveness of the campaign was 56% (25%, 74%), which is consistent with 71% coverage of a vaccine that was estimated as 80.2% effective in the same setting in an unpublished analysis [21], assuming no indirect protection. The programmatic effectiveness among older vaccinees (≥5 years) was 63% (30%, 81%, $P = .002$), and 30% for younger vaccinees (<5 years old), although the latter was not statistically significant ($P = .5$), as there were only 21 cases within this age group. Programmatic effectiveness stratified by time since vaccination appeared higher within 365 days of the campaign (70%; 36%, 86%, $P = .002$), but the study was underpowered to measure campaign effectiveness >365 days after vaccination. Investigators also recently published results of a costing study estimating incremental costs associated with this campaign [22].

This study had several limitations stemming from the COVID-19 pandemic, including disruptions to healthcare seeking behavior, as well as inability to track migration and difficulty in ascertaining individual vaccination status due the halted community survey. Despite this, investigators were able to estimate programmatic effectiveness of the campaign, and the results appear consistent with previously published efficacy and effectiveness estimates. This demonstrates the utility of a TND approach in measuring TCV effectiveness under challenging circumstances. TND has been used previously to assess the effectiveness of influenza, rotavirus, and more recently, COVID-19 vaccines [23–26]. Investigators from the Typhoid Vaccine Acceleration Consortium (TyVAC) recently simulated a matched test-negative design using 3 different test-negative definitions and compared results to those generated as part of a "gold standard" individually randomized controlled trial in Malawi, finding high concordance between results (TND effectiveness estimates ranged from 80.3% to 80.5% as compared to 80.4% efficacy from the randomized trial) [10]. This suggests that TND may be appropriate for measuring TCV effectiveness in the context of an observational study, in spite of design-related concerns about possible confounding and low blood culture sensitivity. TND will also be used as part of an ongoing cluster-randomized trial assessing the effectiveness of another WHO Prequalified TCV, TYPHIBEV® (Vi polysaccharide conjugated to a nontoxic variant of diphtheria toxin [CRM_{197}] carrier protein, Biological E Ltd, Hyderabad, India) in Vellore, India [27]. Similar approaches could be considered for future post-introduction effectiveness evaluations of TCVs to support country demand and uptake of these products.

Questions remain about optimal programmatic use of TCV, including longer-term efficacy and effectiveness conferred by a single dose and how this might vary by initial age of administration [28], but this vaccine is safe, well tolerated, and highly efficacious for at least 3 years following immunization. Decision makers must weigh the value of these immunization programs against other competing health priorities, often without the benefit of subnational incidence and/or AMR data. However, the risk of typhoid fever is not static and is likely to increase due to water scarcity, climate change, and the increasing prevalence of AMR, which elevates the urgency for widespread TCV introduction. In addition, TCVs can be incorporated into multi-antigen campaigns, particularly in areas where routine immunization coverage declined during the COVID-19 pandemic [29]. This study strengthens the case for widespread deployment of TCVs in India and in other typhoid-endemic countries and paves the way for future evaluations of pipeline vaccines. India is slated to introduce TCV with Gavi support [30], which bodes well for advancing health equity and reducing typhoid-related morbidity and mortality across the sub-continent. In light of the growing body of evidence demonstrating the public health value of TCVs, additional typhoid-endemic countries should follow suit.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Global Burden of Disease Collaborative Network. Global Burden of Disease study 2019 (GBD 2019) results. Published 2020. Available at: https://vizhub.healthdata.org/gbd-results/. Accessed 12 February 2023.
2. Carey ME, Jain R, Yousuf M, et al. Spontaneous emergence of azithromycin resistance in independent lineages of *Salmonella* Typhi in Northern India. Clin Infect Dis **2021**; 72:e120–127.
3. Argimón S, Nagaraj G, Shamanna V, et al. Clinical infectious diseases circulation of third-generation cephalosporin resistant *Salmonella* Typhi in Mumbai, India. Clin Infect Dis **2022**; 74:2234–41.
4. da Silva KE, Tanmoy AM, Pragasam AK, et al. The international and intercontinental spread and expansion of antimicrobial-resistant *Salmonella*

Typhi: a genomic epidemiology study. Lancet Microbe **2022**; 3:e567–77.
5. Carey ME, Dyson ZA, Ingle DJ, et al. Global diversity and antimicrobial resistance of typhoid fever pathogens: insights from 13,000 *Salmonella* Typhi genomes. medRxiv. 22283969 [Preprint]. December 30, 2022. Available from: https://doi.org/10.1101/2022.12.28.22283969. Accessed 12 February 2023.
6. Jacob JJ, Pragasam AK, Vasudevan K, et al. *Salmonella* Typhi acquires diverse plasmids from other Enterobacteriaceae to develop cephalosporin resistance. Genomics **2021**; 113:2171–6.
7. World Health Organization. Typhoid vaccines: WHO position paper—March 2018. Wkly Epidemiological Rec **2018**; 13:153–72.
8. SAGE Working Group on Typhoid Vaccines & the WHO Secretariat. *Background paper to SAGE on typhoid vaccine policy recommendations*.
9. Qadri F, Khanam F, Liu X, et al. Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial. Lancet **2021**; 398:675–84.
10. Liang Y, Driscoll AJ, Patel PD, et al. Typhoid conjugate vaccine effectiveness in Malawi: evaluation of a test-negative design using randomised, controlled clinical trial data. Lancet Glob Health **2023**; 11:e136–44.
11. Patel PD, Patel P, Liang Y, et al. Safety and efficacy of a typhoid conjugate vaccine in Malawian children. N Engl J Med **2021**; 385:1104–15.
12. Nampota-Nkomba N, Nyirenda OM, Khonde L, et al. Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomised controlled trial. Lancet Glob Health **2022**; 10:e1326–35.
13. Shakya M, Voysey M, Theiss-Nyland K, et al. Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial. Lancet Glob Health **2021**; 9:e1561–8.
14. World Health Organization. *Global advisory committee on vaccine safety, 5–6 December 2018*.
15. Batool R, Tahir Yousafzai M, Qureshi S, et al. Effectiveness of typhoid conjugate vaccine against culture-confirmed typhoid in a peri-urban setting in Karachi: a case-control study. Vaccine **2021**; 39:5858–65.
16. Yousafzai MT, Karim S, Qureshi S, et al. Effectiveness of typhoid conjugate vaccine against culture-confirmed *Salmonella enterica* serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: a cohort study. Lancet Glob Health **2021**; 9:e1154–62.
17. Lightowler MS, Manangazira P, Nackers F, et al. Effectiveness of typhoid conjugate vaccine in Zimbabwe used in response to an outbreak among children and young adults: a matched case control study. Vaccine **2022**; 40:4199–210.
18. Birger R, Antillón M, Bilcke J, et al. Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study. Lancet Infect Dis **2022**; 22:679–91.
19. Hoffman SA, LeBoa C, Date K, et al. Programmatic effectiveness of a pediatric typhoid conjugate vaccine campaign in Navi Mumbai, India. medRxiv. 22281529 [Preprint]. October 27, 2022. Available at: https://doi.org/10.1101/2022.10.26.22281529. Accessed 12 February 2023.
20. Date K, Shimpi R, Luby S, et al. Decision making and implementation of the first public sector introduction of typhoid conjugate vaccine-Navi Mumbai, India, 2018. Clin Infect Dis **2020**; 71:S172–8.
21. Date KA, Harvey P, Bhatnagar P, et al. LB-5213—field effectiveness of a typhoid conjugate vaccine—Navi Mumbai (India), 2018–2020. In: American Society of Tropical Medicine and Hygiene 2020 National Meeting. **2020**.
22. Song D, Pallas SW, Shimpi R, et al. Delivery cost of the first public sector introduction of typhoid conjugate vaccine in Navi Mumbai, India. PLoS Global Public Health **2023**; 3:e0001396.
23. Flannery B, Chung JR, Monto AS, et al. Influenza vaccine effectiveness in the United States during the 2016–2017 season. Clin Infect Dis **2019**; 68:1798–806.
24. Schwartz LM, Halloran ME, Rowhani-Rahbar A, Neuzil KM, Victor JC. Rotavirus vaccine effectiveness in low-income settings: an evaluation of the test-negative design. Vaccine **2017**; 35:184–90.
25. World Health Organization. *Evaluation of COVID-19 vaccine effectiveness interim guidance*. **2021**.
26. Patel MK, Bergeri I, Bresee JS, et al. Evaluation of post-introduction COVID-19 vaccine effectiveness: summary of interim guidance of the World Health Organization. Vaccine **2021**; 39:4013–24.
27. John J. Vellore Typhoid Vaccine Impact Trial (VEVACT). Available at: clinicaltrials.gov.
28. World Health Organization. Meeting of the strategic advisory group of experts on immunization, April 2022: conclusions and recommendations. Wkly Epidemiological Rec **2022**; 97:261–76.
29. Nampota-Nkomba N, Carey ME, Jamka LP, Fecteau N, Neuzil KM. Using typhoid conjugate vaccines to prevent disease, promote health equity, and counter drug-resistant typhoid fever. Open Forum Infect Dis. Published online 2023.
30. Gavi the Vaccine Alliance. Gavi and Government of India establish new partnership to protect millions of children by 2026. Published 3 February 2023. Available at: https://www.gavi.org/news/media-room/gavi-and-government-india-establish-new-partnership-protect-millions-children-2026. Accessed 24 February 2023.