

Tackling typhoid fever in South Asia: lessons from Vietnam



Biblical diseases like typhoid fever continue to plague South Asia, a densely populated region of 1·8 billion people. Typhoid fever, also known as enteric fever, comprises both typhoid fever (caused by *Salmonella enterica* serotype Typhi [S Typhi]) and paratyphoid fever (caused by *Salmonella enterica* serotype Paratyphi A).¹ The mode of transmission is faecal-oral. All health-care workers in South Asia are familiar with this disease. Because there is no reliable rapid diagnostic test available, many health-care workers use the ubiquitous and antiquated Widal test to make a diagnosis. The Widal test is a serological test that relies on a 4-fold rise in antibody titre against the H and O antigens of S Typhi between the acute and convalescent stages of disease and should be used, if at all, to confirm diagnosis. Instead, it is used as a standalone test which often leads to overdiagnosis of typhoid fever.²

Typhoid fever is the most common blood stream infection in South Asia. The incidence in this region is about 500 per 100 000 population;¹ annually around 7 million people are affected, with about 75 000 deaths.³ The South Asian environment is conducive to the transmission of typhoid fever because of the rapid unplanned urbanisation, urban-rural disparities, poor access to improved water and sanitation facilities, and the common practice of open defecation. The Indian government has intensified efforts to improve sanitation. However, over 134 million people still do not have access to safe drinking water and 68–84% of water sources in South Asia are estimated to be contaminated with bacteria or chemicals, or both.

It is against this backdrop that WHO, in January, 2018, prequalified a new conjugated Vi polysaccharide vaccine, Typbar-TCV, to be rolled out in routine childhood immunisation programmes in countries of endemicity, such as in South Asia.⁴ Although conjugate vaccine efficacy studies in the field are ongoing in Burkina Faso, Malawi, Bangladesh, and Nepal, based on immunogenicity and safety studies in an area of endemicity⁵ (in addition to 87% efficacy shown in a human challenge study,⁶ using a field definition), the Strategic Advisory Group of Experts on immunisation has recommended routine use of the conjugate vaccine in typhoid endemic countries as a single dose in children aged 6–23 months, and for catch-up vaccination in children aged 2–15 years.⁴

This vaccine is the second effective conjugate vaccine that has been studied. In 2001, a study from Vietnam⁷ clearly showed greater than 90% protection using a typhoid conjugate vaccine with *Pseudomonas aeruginosa* as the carrier protein with the Vi polysaccharide antigen. The carrier protein for the new conjugate vaccine is tetanus toxoid. The protective conjugate vaccine studied in Vietnam was not brought to commercial use, probably because it was deemed not lucrative enough for the pharmaceutical company.

The WHO, as early as 2003 in its background document on the diagnosis, treatment, and prevention of typhoid fever, strongly recommended considering the use of typhoid vaccine (the older less effective injectable Vi polysaccharide or the oral typhoid vaccine) in routine immunisation in endemic countries. However, it was mostly the western traveller visiting these countries who received this vaccine. Hence, it is welcome news that Gavi, the Vaccine Alliance, has recently announced that eligible countries (Bangladesh and Nepal, for example) are encouraged to apply for funding to introduce the new typhoid conjugate vaccine into their routine immunisation schedules. Eligible South Asian governments need to give due consideration to this offer.

Although modelling studies have shown the vaccine to be cost-effective⁸ and preventative of antimicrobial resistance, vaccines alone are not adequate to control typhoid fever. Proper sanitation and availability of clean water are crucial. In addition, effective drug treatment of the disease is vital even as a public health measure to avoid transmission of the disease and antimicrobial resistance.

Vaccines will also not be a useful defence against a subset of patients with typhoid fever who become chronic carriers. In these patients, faecal shedding of bacteria continues for several weeks after symptoms have resolved, therefore they are a potential source of infection to others in the community—as Typhoid Mary in New York City in the early 1900s is thought to have been. Longer term treatment with effective antibiotics is necessary.

Vietnam⁹ has a blueprint for tackling typhoid fever in South Asia because it too was a hotbed for the disease. In the early 1990s, the incidence in certain parts reflected that of present day South Asia (ie, about 500 per 100 000 population), but typhoid fever has

almost vanished from Vietnam nowadays. Vietnam introduced projects to improve sanitary conditions with 94% of the 2008 urban population having adequate access to excreta disposal facilities, compared with only 70% in 1995. With tremendous political will, Vietnam carried out a very active vaccination campaign (it even produced its own Vi polysaccharide vaccine) to protect its most vulnerable population against typhoid fever. About 1200 000 children were immunised in 35 provinces. In the 1990s, multidrug resistant S Typhi was highly prevalent in a sentinel hospital in southern Vietnam, and this problem was dealt with comprehensively by treating patients with effective antibiotics. Landmark articles on typhoid fever resulted from Vietnam.¹⁰

From sanitary measures to vaccination to proper treatment, South Asia can learn important lessons from Vietnam regarding the control of typhoid fever. With multidrug-resistant typhoid organisms widespread in parts of Pakistan, there is no time to lose.

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We declare no competing interests.

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- 1 GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis* 2019; **19**: 369–81.
- 2 Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Rev* 2017; **5**: CD008892.
- 3 Mogasale V, Maskery B, Ochiai RL, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *Lancet Glob Health* 2014; **2**: e570–80.
- 4 WHO. Typhoid vaccines: WHO position paper, March 2018—recommendations. *Vaccine* 2019; **37**: 214–16.
- 5 Mohan VK, Varanasi V, Singh A, et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typhbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clin Infect Dis* 2015; **61**: 393–402.
- 6 Jin C, Gibani MM, Moore M, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet* 2017; **390**: 2472–80.
- 7 Lin FY, Ho VA, Khiem HB, et al. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001; **344**: 1263–69.
- 8 Bilcke J, Antillon M, Pieters Z, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *Lancet Infect Dis* 2019; **19**: 728–39.
- 9 Nga TVT, Duy PT, Lan NPH, Chau NVV, Baker S. The control of typhoid fever in Vietnam. *Am J Trop Med Hyg* 2018; **99**: 72–78.
- 10 Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med* 2002; **347**: 1770–82.