

Prevention of enteric fever in travellers with typhoid conjugate vaccines

Highlights

Typhoid fever continues to be a substantial problem in endemic regions and travellers to these regions are also at risk of acquiring this disease. Here we summarise prevention strategies in endemic regions and implications for travellers to these settings considering the availability of novel Vi-conjugate vaccine candidates, and in the current situation of rapidly emerging antimicrobial resistance.

The World Health Organization (WHO) recommends the programmatic use of typhoid vaccines in endemic countries with a high burden of disease to assist with the control of typhoid fever and the escalating problem of antimicrobial resistance. The 2018 WHO position paper on typhoid vaccines indicates preference for the use of new generation typhoid conjugate vaccines (TCVs) over existing parenteral Vi-polysaccharide (Vi-PS) and oral attenuated Ty21a vaccines.¹ Although the highest burden of typhoid fever occurs in older children, aged between 5 and 15 years, 14% to 29% of cases in children occur among those in the under-five year age group.¹ The youngest age group is inadequately covered by the typhoid vaccines that are currently widely available for travellers: the Vi-PS vaccine is indicated for use from the age of two years (as it is poorly immunogenic under 2 years of age) and the oral Ty21a vaccine from five years (as the formulation is not well tolerated in young children). TCVs however, can be used from infancy as T-dependent immune responses are induced by the presence of a carrier protein. Immunogenicity studies have shown that TCVs elicit similar or higher anti-Vi IgG titres than Vi-PS and are immunogenic and well-tolerated in young children from six months of age, but thus far these new generation vaccines are not widely available for international travellers outside India.²

Currently, two TCVs (both conjugated to tetanus-toxoid) are licensed for use in India, however, only one is WHO prequalified (Typbar-TCV, Bharat Biotech, Hyderabad India). This vaccine has been shown to be efficacious in adults challenged with *S. Typhi* in a controlled human infection model.³ Assessment of efficacy in children is currently underway, with active data collection from Phase IIIb effectiveness studies occurring in Nepal, Bangladesh, and Malawi, and there is also a public health introduction of the vaccine in Navi Mumbai, India. These data are expected to substantiate evidence of TCV efficacy in children which has previously been reported for a prototype TCV (Vi-conjugated to recombinant *Pseudomonas aeruginosa* exotoxin A, Vi-rEPA) in children aged between two and six years (87% efficacy at two years [95% CI: 56%, 96%]).⁴

Of the 14 to 21 million cases of typhoid fever that occur each year, the highest burden of disease exists in low and middle-income countries in South Asia, sub-Saharan Africa and South-East Asia.⁵ Over the next decade, countries in South Asia, South-East Asia and Pacific regions are predicted to have the strongest growth in tourist arrivals and travel to Africa is expected to double.⁶ Up to 31% of travellers to these regions will visit friends and relatives. This particular subgroup of travellers has a higher risk of acquiring travel-related infections, with several observational studies showing that more than 85% of typhoid fever cases in returning travellers occurred in individuals who visit friends and relatives. Furthermore, children are disproportionately over-represented among those travellers visiting friends and relatives when compared with other travellers.⁸

While TCV use is expected to decrease the global burden of typhoid fever, the implementation of vaccination programmes will require time. Until control is achieved, travellers, particularly children who visit friends and relatives, will remain at risk of acquiring typhoid infection during travel to endemic regions. Prevention through vaccination and compliance with measures to reduce exposure to contaminated food and water is paramount, particularly in the context of increasing antimicrobial resistance, which reduces treatment options. For the first time in history, infants between the age of 6 months and 2 years can also be protected from typhoid *via* vaccination using TCVs and although minimal data are available regarding the rates of imported typhoid fever in the under two age-group one retrospective study conducted by the Centre for Disease Control, USA reported that 7% of laboratory confirmed *S. Typhi* cases, detected in the United States over a five-year period, occurred in children less than two-years of age.⁹ Using seroincidence data from vaccinees aged six months to 45 years living in a hyper-endemic typhoid region in India¹⁰, Voysey and Pollard estimated TCV efficacy to be 85% [95% CI: 80%, 88%]. This estimate, which is similar to that reported from the prototype Vi-rEPA vaccine, suggests that TCVs are likely to protect at all ages. These vaccines therefore have potential for protection of young travellers, though this is largely not yet realised due to limited availability. Access to next generation typhoid vaccines for international travellers is likely to take time. Despite WHO prequalification and the SAGE recommendation for its use in endemic settings a

shift to TCVs for use in travellers is not likely in the short term as TCVs are not currently available or licensed in Europe or North America and there is currently no indication that the producer is pursuing licensure in high-income settings as yet. In addition to the Vi-tetanus toxoid conjugate vaccines that are currently licensed in India, several other manufacturers have TCVs in various stages of development. (Table 1)

Control of *S. Typhi* through widespread deployment of TCVs, is especially important given the worrying rise of extensively drug resistant (XDR) typhoid strains which have already been reported in Pakistan. Roll out of new programmes in endemic regions will have great benefit for populations suffering a high burden of disease and typhoid control will also benefit travellers to these regions, as exposure risk falls. In the meantime, travellers to typhoid endemic areas should continue to receive typhoid immunisation (Vi-PS or Ty21a or TCV if available in their country) and be advised about measures to reduce the risk of water and foodborne pathogens. Finally, though vaccination provides the potential for relief from typhoid in the near future, new programmes should not distract efforts to control typhoid and other enteric pathogens through provision of clean water and adequate sanitation.

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Table 1. Summary of Typhoid conjugate vaccines in the pipeline

Type	Vi rEPA		Vi TT		Vi CRM ₁₉₇	Vi DT	Vi conjugated to fusion protein PsaA-PdT	O:9-DT
Protein conjugate	Non-toxic recombinant <i>Pseudomonas aeruginosa</i> exotoxin A (rEPA)		Tetanus toxoid (TT)		Non-toxic mutant of diphtheria toxin	Diphtheria toxoid (DT)	Species conserved pneumococcal antigen (SP1572) – penumolysoid (PdT)	O-specific polysaccharides of <i>S.Typhi</i> conjugated to diphtheria toxoid
Developer	National Institute of Health (NIH)	Lanzhou Institute of Biological research and product (China)	Typbar TCV [®] (manufactured by Bharat Biotech)	PedaTyph [™] (manufactured by BIO MED Pvt. Ltd, India)	Biological E	International Vaccine institute (South Korea)/ SK Chemicals, South Korea/ PT BioFarma,	Harvard Medical school	International Vaccine institute

						Indonesia)		
Settings tested	Vietnam		India		India and Pakistan	VaBiotec -	-	-
Phase of trial	Phase 3		Phase 4	Phase 3	Phase 2	Phase 1	Preclinical	Preclinical
Licensure	-		Licensed in India, WHO pre-qualified	Licensed in India	-	-	-	-
Age- group tested	2-15 years		6 months - 45 years	6 months - 12 years	6 weeks - 5 years	-	-	-
Dose	22.5 ug of Vi and 22ug of rEPA in 0.5ml		25 ug of Vi	5 ug of Vi polysacch aride of S. typhi conjugate d to 5 ug of TT.	25 mg of Vi antigen conjugated to CRM ₁₉₇ in 0.5 mL	-	-	-

	2-5 years, 2 doses >5 years, 1 dose	> 6m, 1 dose with a booster after 2 years	< 2 years, 2 doses with a booster at 2 years > 2 years, 1 dose	>6 weeks, 3 doses 9-59 months, 2 doses >59 months, 1 dose			
Compatible with EPI	Unknown	Yes	Yes	Yes(54)	-	-	-

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