Typhoid Conjugate Vaccine: Is It Time for It To Be in the National Immunization Schedule?

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Typhoid is responsible for an estimated 11-21 million cases of febrile illness with 117,000 to 161,000 deaths worldwide annually [1]. Though actual incidence rate of enteric fever in Indian population is lacking, three community-based studies conducted in India between 1995 and 2006 estimated the incidence of culture confirmed typhoid at 377 (178–801) per 100,000 person-years, with the highest incidence in early childhood [2]. The increasing rates of drug resistant *S. typhi*, including Extremely drug resistant (XDR) *S. typhi*, in South Asia is also a cause for concern [3]. World health organization (WHO) recommends programmatic use of typhoid conjugate vaccine to prevent the incidence of typhoid and reduce antimicrobial resistance. This use of vaccine must go hand in hand with other preventive measures, such as improved sanitation, hygiene and access to safe drinking water for a visible reduction in burden of typhoid fever [4]. In India, the typhoid vaccine is not yet a part of the national immunization schedule. The high burden of typhoid in India, the increasing rates of drug-resistant typhoid and the availability of effective conjugate vaccines is likely to alter the vaccination scenario for typhoid.

In the current issue of *Indian Pediatrics*, Kundu, *et al.* [5] have reported an immunogenicity and safety trial of a new typhoid conjugate vaccine (TCV) and compared it with the pre-licensed Typbar-TCV, in healthy Indian children and adults. It was a single blinded, stratified randomized, multicenter, non-inferiority trial and included 240 consenting healthy participants 6 months to 45 years of age; 119 were enrolled in test arm and 121 in the comparator arm. Half of the included participants were children; there were 60 children in both arms. The study subjects were randomized (1:1) to receive intramuscular injection of either 0.5 mL of test vaccine or comparator vaccine, both of which contained 25 µg of purified Vi capsular polysaccharide of *S. typhi* conjugated to tetanus toxoid. Anti-Vi capsular immunoglobulin G titers were measured at baseline and at 6-weeks post

vaccination. Seroconversion rate was found to be 94.8% in test arm and 91.6% in comparator arm. A similar robust rise in geometric mean titers (GMTs) of anti-Vi antibodies post-vaccination was noted in both test and comparator arms. Nearly 34% of participants in the intervention arm and 44% in the comparator arm reported adverse events, with no serious events being reported in both groups.

TCV induces production of antibodies against Vi-capsular antigen of *S. typhi* and high levels of these antibodies correlate with protection against typhoid disease [6,7]. High levels of IgA and higher avidity responses for IgA2 and IgG1 have been shown to be present in the protected individuals receiving TCV in human challenge models [7]. In immunogenicity trials of Vi-vaccines, anti-Vi IgG serves as a marker of protection, though the addition of IgA levels along with its avidity responses would be a potent co-relate of vaccine immunogenicity.

As also pointed out by the authors, this immunogenicity study should be followed up by efficacy trials with larger sample size to detect the actual efficacy of the test vaccine in preventing typhoid fever. Also, post-marketing surveillance will be necessary to detect the rates and types of adverse events when the vaccine will be used in heterogeneous groups of population.

Studies on the licensed TCVs have shown that protection against typhoid persists for about 5 years after vaccination. There is some evidence to suggest that natural boosting occurs in persons living in endemic areas [8]. Till now, there is no evidence whether booster doses are required for the licensed vaccine and the current Indian Academy of Pediatrics Advisory Committee on Vaccine and Immunization Practices (ACVIP) does not recommend a booster [9]. The makers of this new TCV would also have to try and find answers to the questions regarding duration of protection afforded by the index vaccine and need for booster doses. Scheduling the vaccine so that it can fit into the National immunization

schedule is another issue which has to be addressed. The licensed vaccine has been found not to interfere with the immunogenicity of measles vaccine when given simultaneously at nine months of age [4,10] and that could be a potential time for the administration of the TCV.

In conclusion, we appreciate that an equally immunogenic TCV that is at par with the licensed vaccine may be available for use and would help enable programmatic inclusion of typhoid vaccine into the National immunization schedule. However, efficacy trials would be needed to prove that the vaccine prevents typhoid disease in the community setting. The timing of TCV vaccination, especially in relation to the current immunization schedule, the requirement of booster doses, and the ability to be administered concurrently with other vaccines need to be resolved.

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