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# Typhoid Vaccines Ready for Implementation : A History

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Enteric fevers encompass typhoid fever caused by *Salmonella enterica* serotype Typhi (*S.* Typhi) and paratyphoid fever caused by serotype Paratyphi A or B (*S.* Paratyphi). These human-restricted pathogens are acquired by ingesting contaminated water or food, and in the individual patient, one cannot differentiate clinically which agent is causing illness. *S.* Typhi expresses a capsular "Vi" (for virulence) polysaccharide, whereas S. Paratyphi A and B cannot synthesize Vi.

Before the use of antibiotics, typhoid fever had a case fatality rate of 10 to 20%. Transmission of enteric fever is minimized or eliminated if populations have access to treated water supplies and sanitation to remove human fecal matter. Where such amenities are unavailable, the risk of typhoid fever can be substantially diminished by immunization with typhoid vaccines.

Early typhoid vaccines (heat-inactivated whole S. Typhi organisms preserved in phenol) were developed in the 1890s. Six decades later, the World Health Organization (WHO) sponsored large-scale, randomized, controlled field trials, in which investigators found that similar killed whole-cell vaccines conferred substantial protection against typhoid.[1] However, because these vaccines commonly elicited debilitating adverse reactions (fever and malaise), they were rarely used to control endemic typhoid fever.[1]

After a report in 1948 that chloramphenicol drastically ameliorated enteric fevers and reduced the case fatality rate to less than 1%, the treatment



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of patients with oral chloramphenicol became the mainstay of typhoid control in developing countries for the next quarter century. A rude awakening came in the 1970s, when epidemics of chloramphenicol-resistant typhoid occurred in Mexico and Vietnam. These outbreaks stimulated a search for alternative oral antibiotic therapies and accelerated efforts to develop a new generation of better-tolerated, efficacious typhoid vaccines. The efforts bore fruit when live oral *S.* Typhi vaccine strain Ty21a and parenteral Vi polysaccharide vaccine were licensed in the late 1980s and early 1990s. Despite extensive data documenting the safety, efficacy, and practicality of the Vi and Ty21a vaccines, they have not been widely applied programmatically in developing countries.

In the late 1980s, strains of *S.* Typhi that were resistant to multiple clinically relevant antibiotics began to emerge. In response, in 1999, the WHO recommended that typhoid vaccines be used for immunization of school-age children in areas where antibiotic-resistant typhoid was endemic. In 2008, the WHO and the Global Alliance for Vaccines and Immunization took more active steps to encourage programmatic use of these vaccines where typhoid is a health problem.

In most of the world, the incidence of enteric fever peaks among school-age children. However, in some South Asian urban slums, *S.* Typhi bacteremic infections peak in preschoolers, particularly when cases are detected by active household surveillance[2,3]; such infections are uncommon in infants. Since the WHO's Expanded Program on Immunization does not typically include routine visits for toddlers or preschool children, protecting these age groups requires innovative strategies. One approach would be to administer typhoid vaccines in infancy, if efficacy could persist through the preschool and school years. Alternatively, preschool children could be targeted for mass campaigns. The current licensed typhoid vaccines are not compatible with infant immunization, since the unconjugated Vi vaccine is poorly immunogenic in infants, and the use of Ty21a in enteric-coated capsules is impractical.

In this issue of the *Journal*, Sur et al.[4] report results of a well-executed field study showing that the Vi vaccine conferred an adjusted vaccine effectiveness of 80% in preschool children, thereby providing a biologic basis for including preschoolers in mass typhoid-immunization campaigns. However, organizing mass immunizations of so-called noncaptive populations such as preschoolers is more demanding than conducting campaigns among schoolchildren.

Sur et al. showed a trend for a lower adjusted Vi-vaccine effectiveness in older subjects (56% in children between the ages of 5 and 14 years and 46% in persons 15 years of age or older), although the differences in efficacy were not significant. These findings are the opposite of the trend observed in field trials of killed whole-cell parenteral vaccines and of the oral Ty21a vaccine, in which vaccine effectiveness was higher in older children.

A fascinating secondary analysis performed by Sur et al. indicated that control subjects who did not receive the Vi vaccine but lived in clusters with vaccinated subjects had substantial protection against typhoid fever. This is important new information. The indirect protection of nonvaccinated persons by the Vi vaccine further bolsters the case for school-based immunization to control endemic typhoid, since one might expect some indirect protection of preschool children as well. Indirect protection has also been observed with the oral Ty21a vaccine.[1] Both Vi[5] and Ty21a[6] vaccines have been logistically practical and effective when administered to scores of thousands of schoolchildren through large-scale, school-based immunization projects.

An advantage of parenteral Vi vaccine is its single-dose regimen; unconjugated Vi does not elicit immunologic memory, so serum Vi titers are not boosted by additional doses. However, mass administration of the Vi vaccine by needle and syringe creates challenges for ensuring injection safety and for disposing of material that is potentially contaminated with bloodborne viruses. The use of needle-free injection devices could avert this problem. A drawback of the Ty21a vaccine is that it requires a three-dose regimen with an every-other-day interval. Nevertheless, oral immunization is logistically very practical in schoolchildren.

The Vi vaccine does not protect against *S.* Paratyphi A or B, since these strains do not express the Vi polysaccharide. Thus, countries with high rates of paratyphoid fever cannot expect reductions from the use of the Vi vaccine. The Ty21a vaccine confers substantial cross-protection (vaccine effectiveness, 49%) against *S.* Paratyphi B[7] but not against *S.* Paratyphi A.[8]

In computer models, disease incidence and duration of protection greatly affect cost-effectiveness of typhoid vaccination in endemic settings. Field trials of the Vi vaccine have incorporated relatively short follow-up (17 months to 3 years),[9,10] as compared with trials of the Ty21a vaccine (5 to 7 years).[11] Klugman et al.[10] reported a vaccine effectiveness of 55% during 3 years of follow-up. Investigation of a typhoid outbreak among Vi-immunized French soldiers in Africa showed that those who had received the vaccine more than 3 years before exposure had twice the risk of disease, as compared with those who had received the vaccine within the previous 3 years.[12] Three doses of the Ty21a vaccine in enteric-coated capsules conferred a vaccine effectiveness of 62% during 7 years of follow-up.[11]

Two different "flavors" of licensed typhoid vaccine, parenteral unconjugated Vi and oral Ty21a, are available for use by public health practitioners. The time has come to implement use of these vaccines vigorously and monitor the effect of such intervention.

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