Typhoid conjugate vaccines: a step towards typhoid control

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Rabab Batool and colleagues[1] report the efficacy and safety of typhoid vaccines in preventing culture-confirmed *Salmonella* Typhi infections using a systematic review and meta-analysis. The authors find a pooled vaccine efficacy of 83% for the new WHO-approved typhoid conjugate vaccine (TCV) at 1–2 years after vaccination in individuals aged 6 months to 16 years who received a single dose, the highest efficacy among WHO-prequalified typhoid vaccines.

Despite the disease being eliminated from high-income countries, typhoid still causes a huge burden of enteric fever globally, disrupting the lives of children in settings with inadequate quality water and poor sanitation. Increasing antimicrobial resistance and challenging access to medical care in the most resource poor and isolated communities means that typhoid remains a killer. Climate change has been connected to heightened risk of typhoid, and, during the 2022 floods in Pakistan, these new TCVs emerged as potent tools in alleviating the burden of typhoid fever and combating the emergence and spread of drug-resistant *S* Typhi.

There are currently two WHO-prequalified TCVs, which means that WHO considers them appropriate for distribution through international agencies. The first TCV, which is reported in Batool and colleagues' meta-analysis, is a tetanus toxoid conjugate vaccine manufactured by the Indian company Bharat Biotech. The vaccine was recommended by WHO Strategic Advisory Group of Experts on Immunization in October, 2017, for use in endemic countries or in countries with a high burden of antimicrobial resistant *S* Typhi; this was followed closely by the Gavi funding for its introduction in Gavi-eligible countries and WHO-prequalification in January, 2018.[2] The second TCV, a Vi-CRM197 conjugate, manufactured by Biological E (also based in India), was WHO-prequalified in December, 2020, on the basis of a comparable immune response to the previous TCV.[3] Both vaccines are administered as a single dose and can be given to children aged 6 months and older. At the time of writing, six countries with endemic typhoid have already introduced TCV into their routine immunisation schedule, with catch-up to age 16 years in most countries, and more than 56 million children immunised. More countries are expected to introduce TCV in the coming years.

Although the data are encouraging, the meta-analysis found that vaccine efficacy among children younger than 5 years was lower (but still substantial) than that among children aged 5 years and older (73% *vs* 87%). Furthermore, the highest burden of disease is among school-aged children (highest in children aged 5–9 years, followed by children aged 10–14 years) in most studies, and therefore the robust protection across all ages over the first 2 years is very encouraging.[4] Although these differences in efficacy might not be clinically important given the large burden of disease, a key question is whether these findings also affect the duration of protection with a single dose, especially since most future cohorts of children, after the initial campaigns, will be vaccinated following routine immunisation schedules in which the vaccine is given at age 6–15 months. We have shown, in a controlled human infection model of typhoid, that TCV-induced IgA antibodies correlate with protection against deliberate infection of volunteers in Oxford, UK.[5] In field trials in Nepal and Bangladesh, we found that children in the youngest age group (younger than 2 years) had lower IgA responses to TCV than older children (aged 2–16 years).[6,7] Furthermore, some analyses presented at the international invasive Salmonella conference held in Kigali, Uganda indicate that waning over 4–5 years for anti-TCV IgG and IgA antibodies might be more pronounced in the youngest age group.[8,9] While these studies continue with the goal of establishing the duration of immunity and protection following TCVs in South Asia, results from Africa provide some reassurance that longer term protection was observed. Investigators in Malawi conducted an extended TCV trial follow-up and found an overall high efficacy of 78·3% (95% CI 66·3–86·1%) up to 4 years post-vaccination in children aged 9 months to 12 years.[10] If there are differences between study sites in duration of protection, it will be important to understand whether this relates to differences in the force of infection, environmental factors, or genetic differences in immunity.

As more data emerge, there must be a debate about whether booster doses could improve the level and duration of protection; however, for now, the availability and integration of TCV into an increasing number of immunisation programmes over the past 2 years is an immensely important moment for typhoid

control. The technology for TCVs has been available for approximately 40 years, and yet millions of people have continued to become infected and die from the disease. To effectively achieve the goal of typhoid elimination, vaccination efforts must be complemented with ongoing initiatives aimed at improving water and sanitation practices, ensuring accurate diagnosis and treatment of typhoid fever, tackling antimicrobial resistance, and identifying and treating asymptomatic carriers. Indeed, when water is clean, we will not need vaccines for typhoid or many other enteric pathogens.

AJP is chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation and was a member of WHO's Strategic Advisory Group of Experts on Immunization until 2022. AJP has led research at Oxford University on typhoid and paratyphoid vaccines funded by the Bill & Melinda Gates Foundation, the Wellcome Trust, the European Commission, the Medical Research Council, and the Serum Institute of India.

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