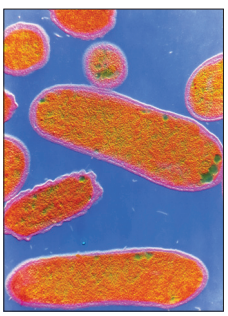
A conjugate vaccine against typhoid fever



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Zulfiqar Bhutta and colleages' study[1] in *The Lancet Infectious Diseases* marks an important milestone for the use of typhoid conjugate vaccines. Present Vi polysaccharide vaccines (Vi-PS) are not widely used because they cannot be given to children younger than 2 years and are thus excluded from the Expanded Programme of Immunization (EPI); furthermore, their effectiveness decreases rapidly after 2–3 years.[2,3] Expectations of a typhoid conjugate vaccine include safe administration to children younger than 2 years, the induction of protective IgG anti-Vi immune responses, and the development of long-term, and at best lifelong, protection. Such an improved vaccine against typhoid fever could have substantial global effect in endemic regions.

Bhutta and colleagues present data from their two phase 2 clinical trials of the immunogenicity and safety of conjugate typhoid vaccine Vi-CRM_{197}. The findings show that the vaccine was safe when given to children younger than 2 years of age, rendering it a suitable candidate for inclusion into EPI programmes. Significant post-vaccination antibody titre concentrations, although largely similar to those of the Vi-PS, were reported. However, those titers were short-lived and substantially decreased after 6 months, which counters expectations of a typhoid conjugate vaccine for sustained long-term antibody titre concentrations. That a booster dose did not yield an additional immune response was surprising and requires, as the authors state, further investigation. Conversely, other Vi-based typhoid conjugate vaccines that are linked to different carrier proteins do seem to elicit long-term protection.[4,5]

This trial was limited to Asian settings (Pakistan, India, and the Philippines). If this vaccine candidate is carried forward to phase 3 trials, African and Latin American study sites should be included. This expansion is especially needed in view of the different levels of immunogenicity and seroconversion rates after booster doses in Pakistani compared with Filipino infants,[1] suggesting the effect of genetic, nutritional, or other environmental factors. In the past few years, standardised activities for surveillance of typhoid fever have been implemented in several sub-Saharan African countries. High-burden sites would allow for such trials to be implemented, and the results of such trials and possible mass vaccinations in high-burden settings, coupled with adequate surveillance data before and after vaccination, would help assess the public health benefit of this new vaccine candidate, including additional effects such as herd immunity.

Several factors have rendered control and management of typhoid fever increasingly difficult. In 2011, the GAVI Alliance reported that no financial support would be provided to countries for the introduction of presently available Vi-PS vaccines, because of insufficient data for disease burden and vaccine effectiveness. The paucity of diagnostic tests that would allow clinicians to rapidly identify causitive pathogens leads to excessive use (even abuse) of antibiotics; drug-resistant strains of *Salmonella enterica* serovar Typhi are becoming progressively prevalent in Africa and Asia.[6-8] Of particular concern is resistance to fluoroquinolones,[6] which leaves physicians facing scenarios in which they can only prescribe from a restricted, often not readily available, selection of antibiotics. Findings from improved and standardised disease surveillance have shown high rates of typhoid fever in Asian[9] and African[10] slums. Less attention has been given to vaccination against typhoid fever because improvement of water and sanitation infrastructure is believed to be the key to long-term prevention and elimination of this disease. Until water and sanitation are upgraded, restriction of the spread of disease through reduction of both disease transmission and emergence of new carriers of typhoid fever is contingent on vaccination. Expansion of vaccination to other high-risk settings should also be considered on the basis of increasing evidence of a noticeable burden of typhoid fever in rural settings in sub-Saharan Africa, which should not be neglected.[11]

Mass vaccinations against typhoid fever have been very effective, and have shown both direct and indirect (herd immunity) protection.[12,13] For successful introduction of any new vaccine, sound epidemiological evidence about burden of disease, combined with vaccine efficacy studies, are a prerequisite to identify appropriate regions and populations to be targeted. The advent of this and other novel typhoid conjugate vaccines constitutes an important event in bringing typhoid fever back to the forefront of public health and in finding avenues for vaccine introduction and inclusion into EPI programmes.

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We declare that we have no conflicts of interest.

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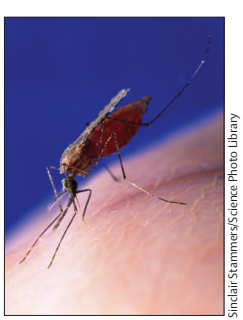
Single low-dose primaquine to reduce malaria transmission

The WHO Evidence Review Group's August, 2012 report about the safety and effectiveness of a single dose of primaquine as a *Plasmodium falciparum* gametocytocide[1] and WHO's new policy recommendation about low-dose primaquine[2,3] generated much interest for malaria control programmes seeking additional methods to reduce malaria transmission, especially in settings in which elimination of malaria is pursued. A single dose of primaquine at 0·75 mg base per kg has long been recommended as an adjunct therapy to reduce malaria transmission of *P falciparum*. However, the drug is often not used because of concerns about dose-dependent haemolytic effects in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and the low availability of G6PD tests in the field. WHO's expert review group reviewed the available scientific literature, which suggested that one low dose of 0·25 mg base per kg of primaquine could be used widely and safely in people with malaria infection, including those with G6PD deficiency,[1] to help reduce the duration of circulating late-stage gametocytes (the sexual transmissible stage of the parasite) by roughly half and contribute to malaria transmission reduction. The authors of the report noted that additional effectiveness and safety evidence would be welcome to characterise the optimum dose and help countries to establish policies and strategies for single low-dose primaquine.[1]

In *The Lancet Infectious Diseases*, Alice Eziefula and colleagues describe the results of the first formal dose-finding study to assess the *P falciparum* gametocytocidal efficacy (measured as duration of gametocyte carriage) of a single dose of primaquine when given with artemisinin combination therapy.[4] The study included 468 Ugandan children younger than 10 years with normal G6PD function and uncomplicated malaria who received standard doses of artemether–lumefantrine and one low dose of primaquine at doses of 0·75 mg/kg, 0·4 mg/kg, and 0·1 mg/kg. The aim was to establish the lowest efficacious dose in people with normal G6PD enzyme function. All doses of primaquine were safe and very well tolerated. The 0·4 mg/kg dose and the standard 0·75 mg/kg regimen had similar gametocytocidal efficacy (mean duration of gametocyte carriage: 6·6 days in the 0·75 mg/kg group and 6·3 days in the 0·4 mg/kg group), but an efficacy gradient was apparent from 0·4 mg/kg to 0·1 mg/kg to placebo. As Eziefula and colleagues note, this work preceded the choice of 0·25 mg/kg in the WHO report,[2] but the WHO-recommended dose falls between the 0·4 mg/kg and 0·1 mg/kg doses



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