Typhoid vaccine development with a human challenge model

Experimental human typhoid fever challenge was first described in 1896 by Wright, who vaccinated two men against typhoid fever and challenged one with what was then known as *Salmonella typhosa*.¹ While challenge models are sometimes controversial, they offer enormous potential to study the pathogenesis of disease and to accelerate vaccine development, particularly in human-restricted pathogens such as *Salmonella enterica* serovar Typhi. The Maryland typhoid human challenge model, which ran from 1952 to 1974, led to insights into typhoid fever and facilitated the development of live attenuated typhoid vaccine Ty21a.²,³ A 21st-century typhoid challenge model has been developed by the Oxford Vaccine Group.⁴

In *The Lancet*, Celina Jin and colleagues⁵ report results from challenging three groups of healthy adults from Oxford, UK, who were randomly assigned to receive Vi-conjugate vaccine, unconjugated Vi-polysaccharide vaccine, or control vaccine (ACYW135 meningococcal conjugate) with wild-type Quailes strain *Salmonella* Typhi. Results of this volunteer challenge have been awaited with much anticipation by the public health community interested in control of typhoid fever in endemic areas of south Asia and sub-Saharan Africa where *S. Typhi* is increasingly antibiotic resistant and few treatment options remain. Vi-conjugate vaccines that have been in development represent a new instrument to help to control typhoid. The most advanced conjugate vaccine, Typbar-TCV (Vi-polysaccharide [Vi-PS] conjugated to tetanus toxoid, Vi-TT, Bharat Biotech, Hyderabad, India), is licensed in India where it has been shown to elicit robust serum Vi antibody responses after only one dose, even in Indian infants as young as 6 months.⁶ In toddlers, older children, and adults, Typbar-TCV was shown to be significantly more immunogenic than the unconjugated Bharat Vi-PS.⁶ Bharat Biotech has submitted an application to WHO for pre-qualification of their Vi-TT vaccine might be higher; for example, a well designed and executed field trial of an unlicensed Vi-conjugate produced by the National Institutes of Health (Bethesda, MD, USA) in Vietnamese pre-school children showed an efficacy of 89% (95% CI 76–97) over 46 months of follow-up.⁷ One possible explanation lies in the primary endpoint of so-called typhoid infection used by Jin and colleagues⁵ (persistent fever ≥38°C for ≥12 h or *S. Typhi* bacteraemia), which arguably is better suited to studying typhoid pathogenesis than assessing the efficacy of typhoid vaccines. Using slightly different endpoints such as fever ≥38°C or higher followed by a positive blood...
culture, similar to surveillance in a field trial and to endpoints used in the Maryland challenge model, Jin and colleagues’ report that the efficacy of Vi-TT was 87·1% (95% CI 47·2–96·9), while efficacy of Vi-PS was 52·3% (-4·2 to 78·2). Although future typhoid challenges based on this as a co-primary endpoint would require larger sample sizes, the information gained might be more relevant and predictive of the efficacy that might be noted in a randomised controlled field trial. This highlights the need for the phase 3 and 4 trials, the first of which is expected to be initiated in Asia in late 2017 by the Typhoid Vaccine Acceleration Consortium (TyVAC), a partnership between the University of Maryland, the University of Oxford, and PATH funded by the Bill & Melinda Gates Foundation. However, because it will be some years before these field trials are reported, Jin and colleagues’ challenge study results are timely and engender optimism that an effective new instrument has become available to help to control typhoid in hyperendemic populations.

*Nicholas A Feasey, Myron M Levine
Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool L3 5QA, UK (NAF); and Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, USA (MML)
nicholas.feasey@lstmmed.ac.uk

NAF declares no competing interests. MML reports co-developing, with colleagues, a Salmonella Enteritidis/Salmonella Typhimurium/Salmonella Typhi Vi trivalent conjugate vaccine against invasive Salmonella disease in sub-Saharan Africa with Bharat Biotech International as a partner and funding from a Strategic Translation Award from the Wellcome Trust. MML has a US patent, 9011871, issued April 21, 2016, for Broad Spectrum Vaccine Against Typhoidal and non-typhoidal Salmonella disease, for which MML along with James E Galen, Raphael Simon, and Sharon Tennant are inventors.

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