The economic case for typhoid conjugate vaccines in countries with medium and high incidence of infection

Published Online
May 23, 2019
http://dx.doi.org/10.1016/S1473-3099(19)30054-4

See Articles page 728

Typhoid fever affects an estimated 11–20 million people globally, causing 128 000–161 000 deaths per year, many of which occur in young children living in resource-limited settings.[1,2] Newly developed typhoid conjugate vaccines (TCVs) are safe, efficacious, and offer durable protection, making TCVs compatible with WHO's Expanded Programme on Immunization (assuming routine vaccination at 9 months of age).[3] However, catch-up campaigns in children up to the age of 5 years or 15 years might also be appropriate, and cost-effectiveness is a critical consideration in choosing the ideal TCV strategy for a given setting.[4] In their study published *The Lancet Infectious Diseases*, Joke Bilcke and colleagues[5] used a comprehensive model of typhoid transmission dynamics, vaccine costs, and epidemiological outcomes to evaluate the cost-effectiveness of alternative TCV delivery strategies in each of the 54 countries eligible for financial support from Gavi, The Vaccine Alliance. The authors concluded that a combined approach (routine immunisation of infants plus a catch-up campaign to the age of 15 years) is likely to be cost-effective in most high-incidence settings (>300 symptomatic cases per 100 000 people per year), whereas no TCV delivery strategy is likely to be cost-effective in low-incidence settings (<30 symptomatic cases per 100 000 annually).

These findings are in broad agreement with those of a separate, independent cost-effectiveness analysis by Lo and colleagues,[6] providing useful guidance to decision makers in high-incidence and low-incidence countries. In medium-incidence settings, however, the situation is less clear. Bilcke and colleagues suggest that the optimal TCV delivery strategy is likely to be all or none—routine immunisation plus a catch-up campaign to age 15 years in most medium-incidence countries and no TCV immunisation at all in a few. By contrast, Lo and colleagues suggest that routine immunisation without catch-up campaigns might be preferred in settings with medium incidence (50–130 symptomatic cases per 100 000 annually) and lower willingness to pay (<US$1000 per disability-adjusted life-year averted). Both analyses agree that the two most important factors in determining the optimal TCV strategy, from a health economic perspective, are typhoid-specific mortality and local willingness-to-pay thresholds, neither of which has been well defined in most countries with medium to high incidence of typhoid.

In most medium-incidence countries, a key policy question will therefore be whether catch-up campaigns should be implemented, and if so, how? For example, such campaigns could be one-off or recurring, delivered at the national or sub-national level, and targeted at all children under a certain age or at specific age groups (eg, those entering elementary school). Importantly, as countries begin to implement TCV, the incidence of typhoid fever would be likely to fall, and the burden of morbidity and mortality would probably shift to older age groups. It might therefore also be important to account for any anticipated cessation of routine TCV immunisation, considering that many medium-incidence countries could become low-incidence within the foreseeable future as a result of TCV implementation and other intervention measures. For these and all other policy questions, cost-effectiveness is only one of many considerations, but it will be important to be forward-looking in future approaches to economic evaluation, moving on from questions of whether to implement TCV immunisation to how, where, and how frequently catch-up campaigns should be done. As Bilcke and colleagues showed, it is in medium-incidence countries that are increasingly willing to pay more for vaccination programmes that the value of additional information (in particular data on typhoid-specific mortality) is greatest. Efforts to implement TCV immunisation should therefore be combined with efforts to collect high-quality data on mortality due to typhoid fever, especially in medium-incidence settings.

In summary, this rigorous model-based study, taken into account alongside other publications, provides strong evidence that TCV vaccines would be cost-effective in Gavi-eligible countries where incidence of typhoid fever is high, and is likely to be cost-effective in most medium-incidence countries. Policy decisions should consider regional variations in typhoid burden and access to care,[7] how current interventions might

For **WHO's Expanded Programme on Immunization** see https://www.who.int/immunization/programmes_systems/supply_chain/benefits_of_immunization/en/

affect the epidemiology of typhoid fever in the future, the feasibility of implementing specific catch-up vaccination strategies, and a careful assessment of willingness to pay. Systems for collecting better data on typhoid-specific mortality should also be prioritised. The high-level economic case for TCV immunisation in countries with medium and high incidence of typhoid fever has been made; it is now time to get down to the details of how to best deliver TCVs to save children's lives.

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The authors declare no competing interests.

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Meningitis: a frequently fatal diagnosis in Africa

See **Articles** page 740

In *The Lancet Infectious Diseases*, Mark W Tenforde and colleagues[1] report the mortality findings of the 2004–15 Botswana national meningitis survey. This was a nationwide laboratory-based audit with linkage to the national HIV and death registries. Data from all patients with culture-confirmed pneumococcal and tuberculous meningitis, and all patients with culture-negative meningitis with CSF white cell count (WCC) above 20 cells per µL were included in their analyses, in addition to a random selection of patients with CSF WCC of up to 20 cells per µL. 10-week and 1-year mortality was 47% (112/238) and 49% (117/238) for pneumococcal meningitis, 46% (22/48) and 56% (27/48) for tuberculous meningitis, and 41% (1181/2900) and 49% (1408/2900) for culture-negative meningitis. Most deaths occurred within the first 10 weeks after lumbar puncture. Across the different diagnostic groups 64–76% of patients had documented HIV infection. Cryptococcal meningitis 1-year mortality of 65% was previously reported from this cohort.[2]

Outside of Africa, linkage of multiple national datasets to improve the understanding of meningitis and other diseases happens more often;[3,4] it is exciting to now see this powerful epidemiological method in use with African datasets, in this report and others.[5] Collection of large-scale, high-quality, routine data in electronic databases has great potential to enhance epidemiological assessment of common diseases, diagnostic and management practices, and outcomes, and to direct and prioritise interventions and inform policy, practice, and research.

The high mortality reported by Tenforde and colleagues[1] is similar to the mortality in other meningitis cohorts in Africa,[6–8] although the lack of details regarding presentation and management in this report (eg, clinical signs and symptoms on presentation, history of length of illness before presenting to hospital, antimicrobial therapy, length of treatment, use of adjuvant therapy) limits the ability to evaluate the major health system contributors. Late presentation, reduced access to optimal diagnostics and antimicrobial therapies, suboptimal acute care, and HIV co-infection have been implicated as major contributors in previous reports.[7,9] Of concern is that over the 12-year period covered by Tenforde and colleagues,[1] HIV was still associated with more than two-thirds of meningitis diagnoses and there was no reduction in meningitis mortality over time, despite the scale-up of antiretroviral therapy in Botswana. Reasons for patients continuing to present with complications of advanced HIV (such as meningitis) despite successful antiretroviral therapy programmes include delayed HIV diagnosis and disengagement from antiretroviral care.[10]

A surprising finding was the high mortality in patients with culture-negative meningitis, regardless of the