Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance

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Typhoid fever is an acute systemic infectious disease responsible for an estimated 12–20 million illnesses and over 150 000 deaths annually. In March, 2018, a new recommendation was issued by WHO for the programmatic use of typhoid conjugate vaccines in endemic countries. Health economic analyses of typhoid vaccines have informed funding decisions and national policies regarding vaccine rollout. However, by focusing only on averted typhoid cases and their associated costs, traditional cost-effectiveness analyses might underestimate crucial benefits of typhoid vaccination programmes, because the potential effect of typhoid vaccines on the treatment of patients with non-specific acute febrile illnesses is not considered. For every true case of typhoid fever, three to 25 patients without typhoid disease are treated with antimicrobials unnecessarily, conservatively amounting to more than 50 million prescriptions per year. Antimicrobials for suspected typhoid might therefore be an important selective pressure for the emergence and spread of antimicrobial resistance globally. We propose that large-scale, more aggressive typhoid vaccination programmes—including catch-up campaigns in children up to 15 years of age, and vaccination in lower incidence settings—have the potential to reduce the overuse of antimicrobials and thereby reduce antimicrobial resistance in many bacterial pathogens. Funding bodies and national governments must therefore consider the potential for broad reductions in antimicrobial use and resistance in decisions related to the rollout of typhoid conjugate vaccines.

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Introduction

Most of the global burden of typhoid occurs in low-income and middle-income countries, particularly in Asia and sub-Saharan Africa.[1,2] Historically, typhoid vaccines have only had modest efficacy, a short duration of protection, and could not be administered to young children, contributing to limited uptake in endemic settings.[3] However, new typhoid conjugate vaccines have shown high and sustained immunogenicity and can safely be given to children as young as 6 months of age, making them suitable for inclusion in national immunisation programmes.[4,5] These vaccines exploit the Vi-polysaccharide capsule conjugated to a carrier protein. Several vaccines of this type are in development and early production, and one (Typbar TCV, Bharat Biotech, Hyderabad, India) was recently prequalified by WHO. In October, 2017, the WHO Strategic Advisory Group of Experts issued new recommendations in support of typhoid conjugate vaccine use in endemic countries, prioritising those countries with high burden of disease or high burden of antimicrobial resistant *Salmonella enterica* serotype Typhi (*S* Typhi).[6] Aligned with these recommendations, Gavi, the Vaccine Alliance, approved US$85 million in funding to support the introduction of typhoid conjugate vaccines.[7] However, governments and Gavi still have decisions to make on future investment, scale of roll out, and how to incorporate the vaccine into current immunisation schedules.[8]

Typhoid fever and the cost-effectiveness of new conjugate vaccines

To inform typhoid conjugate vaccine guidelines and policy decisions, several cost-effectiveness analyses have been made to balance the cost of vaccination with benefits on averting typhoid cases and deaths.[9–11] These cost-effectiveness analyses have projected the effect of various vaccination strategies, including routine immunisation of children and catch-up campaigns, on the number of typhoid cases averted and disability, deaths, and associated costs. Results show that typhoid conjugate vaccines would likely be highly cost-effective in high burden settings (>100 cases per 100 000 population), would sometimes be cost-effective in middle burden settings (10–100 cases per 100 000 population), and less likely to be cost-effective in low burden settings (fewer than 10 cases per 100 000 population). The analyses also found that inclusion of a catch-up campaign for school-age (5–14 years) and younger (1–5 years) children was often a cost-effective strategy. However, typhoid incidence in most endemic countries is uncertain, with substantial geographic and temporal heterogeneity, which poses a challenge towards incorporating typhoid conjugate vaccines into current immunisation programmes and might make adoption less likely. Additionally, concerns remain about whether vaccination would reduce overall clinical disease burden but increase sub-clinical disease, continuing to drive overall transmission, which would require monitoring.[5]

The standard approach of evaluating only the disease-specific economic and health effects of new conjugate vaccines could overlook other potentially substantial benefits that are unique to immunisation against typhoid fever. Recently, several economists and public health experts argued that traditional approaches in vaccine evaluation might dramatically underestimate their health and economic benefits, by focusing on direct medical costs

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and loss of productivity for individuals with the vaccine-preventable illness.[12,13] In particular, they note that broader outcomes such as averted antimicrobial resistance, school attendance, labour participation, and reduction in inequality by wealth are not adequately captured in traditional cost-effectiveness models of vaccination.[14] The effect of typhoid vaccination campaigns might be similarly undervalued if key outcomes are not captured in the cost-effectiveness calculations. Here, we focus on avertable use of antimicrobials and rising antimicrobial resistance among typhoidal salmonella and, perhaps more importantly, among other bacterial illnesses. Historically, the emergence of multidrug-resistant *S* Typhi was associated with increased mortality, requiring a shift to newer antimicrobials.[15] Now, even more highly resistant *S* Typhi and *Salmonella enterica* serotype Paratyphi (*S* Paratyphi) have been reported, which could lead to rising rates of morbidity and mortality due to typhoid fever.[16–19] Crucially, antimicrobial use targeted at typhoid fever might be an important driver of selective pressure for antimicrobial resistance in other organisms; therefore, antimicrobial resistance should be an important point to consider when making policy decisions about the introduction of new typhoid conjugate vaccines.

The effect of typhoid fever on antimicrobial resistance in other bacterial illnesses

Although typhoid fever is an important, invasive bacterial infection in many endemic regions, typhoid commonly only accounts for a minority of febrile disease presentations to clinics and hospitals in these settings. Large surveillance studies from Asia and Africa found that only 1–4% of individuals suspected to have typhoid fever (ie, fever for ≥3 days as defined by WHO)[20] had culture-confirmed typhoid.[21,22] Because untreated typhoid leads to an increased risk of morbidity and mortality (potentially with up to a 25% case fatality rate) and diagnostic testing is limited because of poor sensitivity, clinicians in typhoid-endemic settings frequently administer empirical antimicrobial therapy to patients with suspected typhoid fever. Consequently, the regional presence of typhoid fever often results in substantial overtreatment of typhoid with unnecessary antimicrobials, which might indirectly drive the increasing resistance to antimicrobials in typhoidal salmonella and potentially other bacterial infectious diseases. In a 2017 prospective study[23] originating in Nepal, more than 20 patients were treated for typhoid fever for every one patient with culture-confirmed typhoid. A recent meta-analysis from India[24] found that since the year 2000, less than 3% of individuals with suspected typhoid fever had a culture-confirmed infection. In the ongoing Surveillance of Enteric Fever in Asia Project, in which there is surveillance for acute febrile illnesses at hospitals in Pakistan, Nepal, and Bangladesh, five to ten patients are diagnosed with typhoid fever for every culture-confirmed case (unpublished). Even after adjusting for the sensitivity of the culture (61% in a recent meta-analysis),[25] data show that between three and 25 patients are treated for suspected typhoid fever for each true case, depending on regional variations in epidemiology and health-care practices. These findings are consistent with studies from India and Africa (figure). Moreover, household surveys suggest that in many settings, most patients with febrile illness are treated at pharmacies or medical shops, where diagnostic testing is rare and use of antimicrobials is unrestricted, although this can differ substantially by location.[29,30] This unrestricted use suggests that even more antimicrobials are being used to treat suspected typhoid fever.[29,30] Based on existing findings and global estimates of typhoid disease incidence at 12–20 million,[1,2] we conservatively estimate that more than 50 million individuals are treated annually with antimicrobials on the suspicion of having typhoid fever.

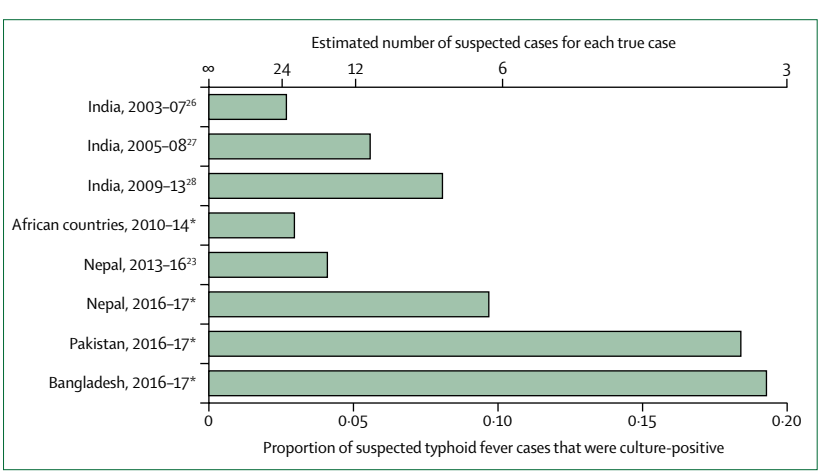

Figure: **Proportion of suspected typhoid fever cases that were culture-positive, and the estimated number of suspected typhoid cases for each true case**
The number of suspected typhoid cases for each true case were estimated by dividing the inverse of the culture-positive proportion by the sensitivity of the culture, estimated from a meta-analysis.[25] Studies with data from the past 10 years,[23,26–28] and unpublished data from the authors' ongoing prospective cohort studies were included, and indicate that many patients with suspected typhoid are treated for each true case. *Unpublished.

Overtreatment of typhoid fever might be rational on an individual level, especially given the risks associated with untreated typhoid and the issues surrounding the care and follow-up of patients living in low-income and middle-income countries. However, there might be more substantial implications of typhoid fever overtreatment at a population level. The widespread use of antimicrobials for treatment of patients with suspected typhoid disease increases the selective pressure for the emergence and spread of resistant bacteria. South Asia, the region with a large portion of the world's typhoid burden, is already struggling with high rates of antimicrobial resistance in some pathogenic bacteria, and recent phylogeographic studies have shown that many antimicrobial-resistant enteric pathogens disseminate globally from the Indian subcontinent.[31,32] Data suggest that suspected typhoid (ie, non-specific febrile disease) might be one of the largest drivers of

antimicrobial use across south Asia, and therefore might be a major driver of antimicrobial resistance in bacterial pathogens across the region. There is a precedent for using vaccines to reduce the selective pressure for bacteria. The recent introduction of the pneumococcal conjugate vaccine[33,34] was estimated to have reduced the incidence of antimicrobial-resistant infections substantially, and to have prevented millions of days of antimicrobial use in young children.

Overtreatment of typhoid also leads to increased health-care costs and poorer infection outcomes. Many studies have shown that most individuals receiving antibiotics for a febrile illness actually have a viral infection.[35,36] For these patients, antibiotics provide no clinical benefit, but increase costs and risks of side-effects and toxic effects, while also disrupting the human microbiome, which can have downstream health effects. Because suspected cases of typhoid fever typically far outnumber true cases of typhoid fever, the costs and health effects associated with true typhoid cases might be far greater than those captured in economic analyses, which often only consider confirmed typhoid cases. The costs and health effects of empirically treating typhoid might increase dramatically soon, because typhoidal salmonella is becoming increasingly resistant to the most effective oral antimicrobial drugs.[19,37] This increasing resistance to oral antimicrobials might also result in more frequent hospitalisation for individuals with suspected typhoid fever, for treatment with more expensive intravenous antimicrobials, which brings an additional risk of nosocomial infection. Finally, patients with presumed typhoid that have a different bacterial infection (eg, rickettsial infections, leptospirosis) need to urgently receive the right treatment. This issue was brought to attention in a recent trial from Nepal,[38] in which patients who were culture-negative for typhoid had inferior outcomes when treated for typhoid using ceftriaxone. Empirical treatments for typhoid could delay the administration of a therapy that is effective for other bacterial infections.

Vaccination strategies must reduce typhoid incidence and associated antimicrobial use

Until the incidence of typhoid fever has been reduced to a level at which empiric antibiotic treatment of acute febrile illnesses for suspected typhoid is no longer necessary, there will likely be minimal changes in antimicrobial prescribing practices. Because of the substantial risk of morbidity and mortality that is associated with typhoid, clinicians and health-care workers in low-income and middle-income countries might continue to accept overtreatment of patients presenting with a febrile disease, to avoid missing a true case of typhoid. Therefore, vaccination strategies must reduce typhoid incidence below the perceived threshold that most clinicians are using to determine whether to treat patients for suspected typhoid. Furthermore, public perception of antimicrobial therapy will also factor into changes in overall prescription patterns.

Reducing overtreatment would likely first require disease surveillance (eg, sustained blood culture surveillance programmes) to monitor the incidence of typhoid and other bacterial infections (eg, *S* Paratyphi and invasive non-typhoidal salmonella). Subsequently, education and public health campaigning might help change the perception of clinicians and the public. Despite these challenges, historical evidence suggests that a reduction in typhoid incidence through vaccination will be accompanied by changes in clinical practice towards patients with febrile illness. Over the past three decades, typhoid has been gradually considered less of a public health problem in South America,[39,40] causing fewer clinicians in this region to treat patients with febrile illness empirically for typhoid, thus reducing unnecessary use of antimicrobials.

One example of how an intervention has changed clinical practice is the roll out of rapid malaria diagnostic tests in endemic regions, which have shown a lower malaria burden than previously thought in many settings, and led to fewer prescriptions of antimalarials.[41,42] However, the intervention might also have had the unintended consequence of increasing antimicrobial prescriptions, in place of the antimalarials.[41,42] Overall, these historical examples do support the idea that a reduction in typhoid incidence could lead to a sizeable decline in the use of antimicrobials.

A key question remains: if typhoid burden is reduced, will clinicians or the informal health-care sector simply use an alternative bacterial diagnosis, thereby continuing to prescribe a broad range antimicrobial? In south Asia, typhoid fever accounts for a substantial proportion of community-acquired bacteraemia cases. However, enteric fever caused by *S* Paratyphi A (for which current typhoid conjugate vaccines are not effective) can account for a large proportion of cases in this region,[43] and rickettsial infections and leptospirosis are also common causes of acute febrile illness in these settings, but are under-reported and not treated empirically as frequently as typhoid fever. Invasive non-typhoid salmonella infections, which are uncommon in south Asia, were the second most common cause of community-acquired bacteraemia in a 2017 study in ten African countries,[22] especially in Burkina Faso and Ghana. Therefore, the effect of reduced typhoid incidence on antimicrobial prescribing practices might differ by setting, depending on the local epidemiology. Regions with a low incidence of other endemic bacterial illnesses would be expected to benefit the most from typhoid vaccination programmes that reduce the need for empirical antimicrobial therapy. Regions with a higher incidence of other salmonella infections (*S* Paratyphi A in parts of South Asia, invasive non-typhoidal salmonella in parts of sub-Saharan Africa) or bacterial illnesses might benefit less. Furthermore, clinicians might continue to use antibiotics for empirical

treatment of acute febrile illness, even after typhoid disappears, by targeting other bacterial infections. Vaccines are under development for invasive non-typhoidal salmonella; in a similar manner to typhoid fever, settings in which invasive non-typhoidal salmonella infections are endemic might also observe a decline in antimicrobial use with the introduction of vaccines. Although vaccines for *S* Paratyphi, non-typhoidal salmonella, and other invasive bacterial infections are greatly needed, we anticipate that removing typhoid as the leading bacterial cause of acute febrile illness could still have a substantial effect on antimicrobial prescribing practices in the regions with endemic typhoid. This change in antimicrobial prescribing practices can be measured to determine the success of typhoid vaccination programmes.

Implications for policy, financing, and research decisions for typhoid conjugate vaccines

Key funding and country-level decisions are being made about whether and how to incorporate typhoid conjugate vaccination in public health systems in typhoid-endemic countries. Despite the challenges in quantifying the true health and economic effects of typhoid vaccination, ignoring the substantial costs and health effects of antimicrobial use and antimicrobial resistance associated with typhoid would lead to underestimating the value of these vaccines. Antimicrobial prescribing practices for febrile illness (and other health-care practices) should be considered an important metric to assess the true impact of typhoid conjugate vaccination in public health systems. Ongoing and upcoming vaccine effectiveness studies provide a unique opportunity to assess this outcome.[8]

The widespread use of antimicrobials for typhoid fever, compared with the low prevalence of disease among patients with suspected typhoid fever, suggests that the threshold for clinicians to initiate treatment for typhoid is low. Few spillover health and economic benefits will be accrued until typhoid incidence is driven below this threshold, and there are substantial policy implications about vaccine implementation in terms of scale and target populations that suggest the need for more aggressive vaccination strategies. An expanded vaccination strategy might therefore be necessary to overcome the drivers of suspected typhoid fever overtreatment. To achieve greater and more rapid reductions in typhoid incidence and antimicrobial use, policy makers and governments could opt for catch-up vaccination campaigns for school-age (5–14 years) and younger (1–5 years) children, in addition to introducing typhoid vaccines through routine immunisation programmes. In many south Asian cities with a high incidence of typhoid, driving incidence down sufficiently to change empirical antimicrobial prescription practices will likely require high typhoid vaccine coverage in addition to disease surveillance, and consideration for challenges such as migration, which might introduce new infections and non-immune people that change overall population susceptibility and transmission.[44]

Typhoid vaccines provide a unique opportunity to substantially reduce empirical use of antimicrobials, and to curb the global dissemination of antimicrobial resistance in many other bacterial pathogens apart from *S* Typhi. However, we believe that these benefits will only be obtained if typhoid incidence is driven below a threshold that can affect clinical practice, and if public health campaigning can help change public perception of antimicrobials. We propose that vaccination programmes that achieve these substantial reductions in typhoid incidence (likely by including catch-up campaigns) might have substantial beneficial effects on antimicrobial use and resistance that are currently being missed. These beneficial effects should be considered in both global and country-level decisions on vaccine roll out, and data collection should track use of generic antimicrobials for febrile illness as a metric for progress. Countries with endemic typhoid, and funding bodies that are considering scaling up their typhoid conjugate vaccine programmes, have a unique opportunity to address both the global burden of typhoid and the global burden of antimicrobial resistance.

Contributors

JRA conceived the Personal View. All authors contributed to the creation of content and approved the final draft. JRA had full access to all the data, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

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