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Meiring, J.E. orcid.org/0000-0001-9183-5174, Giubilini, A., Savulescu, J. et al. (2 more authors) (2019) Generating the evidence for typhoid vaccine introduction: considerations for global disease burden estimates and vaccine testing through human challenge. *Clinical Infectious Diseases*, 69 (Supplement_5). S402-S407. ISSN 1058-4838

<https://doi.org/10.1093/cid/ciz630>

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Generating the Evidence for Typhoid Vaccine Introduction: Considerations for Global Disease Burden Estimates and Vaccine Testing Through Human Challenge

James E. Meiring,^{1,2} Alberto Giubilini,³ Julian Savulescu,³ Virginia E. Pitzer,⁴ and Andrew J. Pollard^{1,2}

¹Oxford Vaccine Group, Department of Paediatrics, University of Oxford, ²National Institute for Health Research Oxford Biomedical Research Centre, and ³Oxford Uehiro Centre for Practical Ethics, University of Oxford, United Kingdom; and ⁴Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, Connecticut

Typhoid fever has had a major impact on human populations, with the causative pathogen *Salmonella enterica* serovar Typhi implicated in many outbreaks through history. The current burden of disease is estimated at 11–18 million infections annually, with the majority of infections located in Africa and South Asia. Data that have been used to estimate burden are limited to a small number of blood-culture surveillance studies, largely from densely populated urban centers. Extrapolating these data to estimate disease burden within and across countries highlights the lack of precision in global figures. A number of approaches have been developed, characterizing different geographical areas by water-based risk factors for typhoid infection or broader measures of health and development to more accurately extrapolate incidence. Recognition of the substantial disease burden is essential for policy-makers considering vaccine introduction. Typhoid vaccines have been in development for >100 years. The Vi polysaccharide (ViPS) and Ty21a vaccines have had a World Health Organization (WHO) recommendation for programmatic use in countries with high burden for 10 years, with 1 ViPS vaccine also having WHO prequalification. Despite this, uptake and introduction of these vaccines has been minimal. The development of a controlled human infection model (CHIM) enabled the accelerated testing of the newly WHO-prequalified ViPS–tetanus toxoid protein conjugate vaccine, providing efficacy estimates for the vaccine, prior to larger field trials. There is an urgency to the global control of enteric fever due to the escalating problem of antimicrobial resistance. With more accurate burden of disease estimates and a vaccine showing efficacy in CHIM, that control is now a possibility.

Keywords. typhoid; vaccines; human challenge; epidemiology; infectious diseases.

Typhoid fever, caused by the ingestion and subsequent mucosal invasion of the pathogen *Salmonella enterica* serovar Typhi (*S. Typhi*), is a serious public health concern in many low- and middle-income countries (LMICs), with an estimated global burden of 11–18 million infections annually [1–3]. In addition, the pathogens *Salmonella enterica* serovars Paratyphi A, B, and C (*S. Paratyphi*), which have a similar clinical presentation to that of *S. Typhi*, are responsible for an estimated 3.4–5.4 million infections globally per year [3, 4].

While improvements in drinking water quality and sanitation have all but eradicated the disease from the majority of developed countries [5–7], short- to medium-term control of the pathogen through vaccination is widely accepted as the best strategy for reducing disease burden in low-income settings [8–10]. Escalating antimicrobial resistance throughout the world, including the 2016–2019 extensively drug-resistant outbreak of *S. Typhi* in

Pakistan, threatens the gains in typhoid control and creates concern of a return to the preantibiotic era [11, 12].

However, the generation of evidence to support introduction of an efficacious vaccine against *S. Typhi* into the world's endemic countries has encountered many challenges. With a nonspecific clinical presentation and no reliable point-of-care diagnostic, predicting accurate disease burden—and therefore demonstrating the need for vaccination to prevent morbidity, mortality, and economic burden—has been problematic.

In addition, with a human-restricted pathogen such as *S. Typhi*, determining the efficacy of new vaccines has been slow, requiring large field trials, which are both expensive and time-consuming. To accelerate vaccine testing, a controlled human infection model (CHIM) for both *S. Typhi* and *S. Paratyphi* has been developed in Oxford, United Kingdom [13–15]. This model has enabled the efficacy testing of a number of candidate vaccines [16], including the recently World Health Organization (WHO)-prequalified typhoid Vi polysaccharide protein conjugate vaccine (Vi-TT) [17, 18], providing data used to support the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommendation in 2017 for use of typhoid conjugate vaccines (TCVs) in high-burden countries and the Gavi commitment for funding the introduction of TCVs into eligible countries [19, 20].

Correspondence: J. E. Meiring, Oxford Vaccine Group, CCVTM, Churchill Hospital, Headington, Oxford OX3 7LE (james.meiring@paediatrics.ox.ac.uk).

Clinical Infectious Diseases® 2019;69(S5):S402–7

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In this article, we discuss some of the necessary components for the introduction of typhoid vaccines. We bring together the latest approaches for predicting typhoid burden and vaccine impact with a summary of past and current enteric fever vaccines in development, including the ethical requirements surrounding the CHIM used to enable typhoid vaccine efficacy trials.

Predicting Typhoid Burden and Vaccine Impact

The burden of typhoid fever—that is, the incidence of disease, the severity of illness, the costs to individuals and health systems to treat it, and the extent of antimicrobial resistance—is a key element underlying the need for TCVs and decisions about how best to deploy them. However, the burden of typhoid fever is difficult to quantify. The symptoms of the disease, including prolonged fever and abdominal discomfort, are non-specific and easily confused with other potential diagnoses [21]. Confirmation of typhoid cases currently relies upon blood culture, which is difficult to implement in many low-income settings and suffers from poor sensitivity [22].

Typhoid incidence was directly assessed in only 22 sites in 14 different countries between 1980 and 2017, with the recent Typhoid Surveillance in Africa Program adding additional data from 13 sites across 10 African countries [1, 23, 24]. The limited geographical breadth of burden data presents challenges when trying to extrapolate from data for just a few sites to estimate the global incidence of typhoid fever. A variety of approaches have been used to estimate the incidence of typhoid fever from the available data. Some models have estimated the incidence by region and assumed that incidence is similar in nearby regions without data [2, 4, 25], with or without adjusting for typhoid risk factors, including the percentage of the population living in urban slums and rural locations without access to improved water [2]. Other studies used the available data to identify the best predictors of typhoid fever incidence from a variety of possible covariates [1, 3]. One such study found that general measures of health (eg, prevalence of stunting) and development (eg, percentage of roads paved, percentage of the population living in extreme poverty) were more predictive of typhoid fever incidence than widely used measures of access to improved water and sanitation [1]. As a result of the different methods used, estimates of typhoid incidence have shown considerable variation, particularly for countries with few or no data [26]. Furthermore, typhoid incidence has been known to change over time—sometimes dramatically—as evidenced by recent multiyear outbreaks that have been occurring across parts of sub-Saharan Africa associated with the emergence of antimicrobial-resistant strains [27].

For countries without surveillance data, the recently published WHO Surveillance Standards for Vaccine-Preventable Diseases advise that the minimum surveillance for typhoid-endemic countries should be laboratory or facility based [28]. This could be either the routine passive reporting of positive

laboratory results for invasive *Salmonella* to a surveillance system, or an active approach where patients meeting set criteria are identified in a number of sentinel facilities for blood culture collection. While this method of surveillance would not identify all the cases of enteric fever within a population, it would allow disease patterns to be monitored over time, both pre- and postvaccine introduction. This approach has been well demonstrated from sentinel surveillance sites in some LMICs [29]. It could also be integrated with other disease reporting systems already operating within the country and would allow the reporting of antimicrobial susceptibility data. It would also be of added benefit to choose surveillance sites from different contexts within the country (eg, urban vs rural).

Published data from Bangladesh have provided an example of how this might be achieved [30]. Using the Global Invasive Bacterial Vaccine-Preventable Diseases Surveillance Network designed for pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, clinicians expanded the inclusion criteria for blood culture collection in children admitted to sentinel hospital facilities to perform typhoid surveillance. This resulted in a 25% increase in number of blood cultures performed, but a 5-fold increase in detection of enteric fever cases. This was introduced with only a modest increase in costs of US\$44 974 annually. For countries wanting to establish typhoid fever surveillance and to monitor impact of vaccine, this may provide a platform that is both affordable and implementable.

To assess the value of typhoid vaccination strategies, it is also important to know severity and costs associated with typhoid illness. The hospitalization and case fatality rates are particularly influential when estimating the cost-effectiveness of typhoid vaccination strategies [31–33]. However, studies have found considerable heterogeneity in the hospitalization and case fatality rates of typhoid fever cases in different parts of the world [34, 35]. In particular, estimates of the case fatality rate that are derived only from blood culture-confirmed patients may overestimate the mortality rate, as these cases could represent the more severe end of the spectrum of illness. Conversely, typhoid cases with intestinal perforations tend to exhibit higher case fatality rates [36], but fatal intestinal perforation cases may have lower rates of blood culture confirmation. Estimates of the costs of treating typhoid fever are also highly variable [37], and few studies have measured the costs to individual patients themselves. The impact of antimicrobial resistance should also be factored into these cost estimates.

TCVs are likely to provide protection not only for those who receive the vaccine, but also indirect protection (ie, herd immunity) by reducing typhoid transmission [38]. Mathematical models of typhoid transmission have been developed to predict the population-level impact of different vaccination strategies against typhoid fever [31, 32, 39]. These models generally predict that the benefits of a population-wide vaccination strategy will exceed the reduction in incidence expected among

vaccinated individuals alone. However, the level of indirect protection is difficult to predict and will depend on the ability of TCVs to prevent not only typhoid fever, but also shedding of the bacteria from subclinical cases [38]. Mathematical models attempt to infer the prevalence of infection from the observed cases of disease and understanding of the natural history of the pathogen, but are difficult to validate. The prevalence of chronic carriers and the role they play in transmission will influence the predicted level of indirect protection from vaccination [39, 40].

Enteric Fever Vaccines: Development and Clinical Testing

Development of enteric fever vaccines started in the late 19th century with the first heat-killed vaccines (see also Gradmann et al., S385 in this supplement) [41]. In the 1950–1960s, whole cell vaccines (WCVs) went through a number of efficacy trials, with a meta-analysis suggesting a cumulative 3-year efficacy of 73% [42] with introduction of 1 WCV into the Expanded Programme on Immunization in Thailand [43]. Unfortunately, this vaccine caused high rates of systemic and localized side effects, leading to school absenteeism in children [44].

In the 1970–1980s, 2 additional vaccines were developed. Ty21a is an oral live attenuated vaccine that went on to large-scale field trials after showing promising efficacy results (87% after 5–8 doses) in a CHIM in Maryland (see also Kirchhelle et al., S388 in this supplement) [45]. Meta-analysis of these trials demonstrated a cumulative efficacy of 50% at 3 years [42, 46]. Analysis from these trials also demonstrated an estimated protective efficacy against *S. Paratyphi B* of 45% (95% confidence interval [CI], 8%–73%) [47].

Vi polysaccharide (ViPS) is a parenteral vaccine containing the purified capsular ViPS antigen. Combining results from individually and cluster randomized trials, efficacy at 2 years for ViPS was 59% [46]. ViPS is not licensed in children <2 years of age due to poor immunogenicity. Because the vaccine contains a T-cell-independent antigen, it does not induce immunological memory and cannot be boosted with repeated vaccination [48].

However, conjugate vaccines, where the polysaccharide capsule is chemically conjugated to a protein carrier, do produce a T-cell-dependent response [49–51]. This technology has now been applied to both the Vi antigen, with a number of TCVs in various stages of development, and the O-specific polysaccharide from *S. Paratyphi A*. Vaccines in clinical testing are summarized in Table 1.

Typhoid CHIM: Enabling Vaccine Testing

The most widely used TCV, Typbar-TCV (Bharat Biotech, India), first licensed for use in India, received WHO prequalification in January 2018 [17], supported by efficacy data from the Oxford CHIM. In this study, 112 healthy participants received either Vi-TT, ViPS, or a control meningococcal vaccine in a 1:1:1 double-blind randomization. One month following vaccination, participants were orally challenged with *S. Typhi* bacteria and were followed up

as previously described [13]. From this model, the protective efficacy (PE) of Vi-TT against typhoid infection (defined as persistent fever or bacteremia) was 54.6% (95% CI, 26.8%–71.8%), which was comparable with the PE of ViPS at 52% (95% CI, 23.2%–70.0%). In the model, following oral challenge with the pathogen, participants have blood culture collection daily for the subsequent 14 days regardless of symptoms. In field settings, a participant would only have blood culture collection after the development of fever. Applying this case definition of fever followed by the identification of bacteremia, which may more closely simulate a “real-world” field trial, PE of Vi-TT increased to 87.1% (95% CI, 47.2%–96.9%) compared with 52.3% (–4.2% to 78.2%) for ViPS [18].

TCVs now have a WHO SAGE recommendation for use from 6 months of age in typhoid-endemic regions, with routine introduction to be prioritized in countries with high burden of disease and/or high rates of antimicrobial resistance [19, 48] and commitment from Gavi to fund introduction into eligible countries, with field trials under way providing the data to inform this implementation [8, 20, 65]. There remains a need for vaccines against *S. Paratyphi A*, and the paratyphoid model also developed in Oxford may prove useful in further vaccine testing [14].

For pathogens like *S. Typhi*, the use of CHIM has the potential to accelerate vaccine evaluation and introduction [66]. It has proven to be a valuable tool in this case, among a wider toolkit of additional measures including field trials and immunogenicity data [61]. There are important ethical points that must be considered in the development and use of any CHIM. In challenge studies, participants are intentionally exposed to a risk to benefit scientific research and therefore the risk must be worth taking and sufficiently small. The risk should therefore be known before commencing the study; nonhuman or epidemiological work should be performed to estimate risk and show the necessity of human subjects. In addition, the risk must be proportionate to the expected benefits of the study and “under no circumstances should the research expose volunteers to risks of irreversible, incurable or possibly fatal infections” [67–69]. Participation in the study must be free and autonomous, with reimbursement for time and travel. Participants should understand all the risks involved, the potential benefits, and the options they have for opting out. Successfully applying these conditions to the challenge of humans with *S. Typhi* has enabled the safe and rapid testing of vaccines described in this review.

CONCLUSIONS

Through the use of mathematical modeling and extrapolation of incidence data across nonsurveyed regions, typhoid burden estimates, including case fatality rates and the impact of antimicrobial resistance, are becoming more robust. Combining these data with cost-effectiveness estimates, the case for vaccine

Table 1. Typhoid and Paratyphoid Conjugate Vaccines, Licensed or in Late-stage Clinical Development

Vaccine	Vi-rEPA ^a	Vi-DT	Vi-CRM ₁₉₇	Vi-TT (PedaTyph)	Vi-TT (Tybar-TCV)	O:2-TT
Pathogen target	<i>S. Typhi</i>	<i>S. Typhi</i>	<i>S. Typhi</i>	<i>S. Typhi</i>	<i>S. Typhi</i>	<i>S. Paratyphi A</i>
Carrier protein	Recombinant <i>Pseudomonas aeruginosa</i> exoprotein A	Diphtheria toxoid	Diphtheria toxin CRM ₁₉₇	Tetanus toxoid	Tetanus toxoid	Tetanus toxoid
Clinical trials (n = 14)						
Safety and immunogenicity	18–44 years of age, US [52]; 2–44 years of age, Vietnam [53]	2–45 years of age, Philippines [54]; 2–40 years of age, Indonesia [55]	18–40 years of age, Belgium [56]; 6 weeks to 45 years of age, Pakistan, India, and Philippines [57]	3 months to 5 years of age, India [58, 59]; 6 months to 12 years of age, India [60]	6 months to 45 years of age, India [61]; 18–60 years of age, UK [18]	2–44 years of age, Vietnam [62]
Efficacy	2–5 years of age, Vietnam; protective efficacy 91.5% at 27 months, 89% at 47 months [63, 64]	None	None	6 months to 12 years of age, India; protective efficacy 100% ^b (95% CI, 97.6%–100%) at 12 months [60]	18–60 years of age, UK; protective efficacy 54.6%–87.1% at 14 days [18]	None
Developer(s)	US NIH; Lanzhou Institute of Biological Products, China	International Vaccine Institute, Korea; SK Bioscience, Korea; Bio Farma, Indonesia	GSK Vaccines for Global Health, Italy; Biological E, India	Bio Med, India	Bharat Biotech, India	US NIH; Changchun Institute of Biological Products, China; Lanzhou Institute of Biological Products, China
Licensed	India	India, Nepal, Pakistan, Zimbabwe, Nigeria, Cambodia	...

Abbreviations: CI, confidence interval; NIH, National Institutes of Health; O:2-TT, O-specific polysaccharide-tetanus toxoid; TCV, typhoid conjugate vaccine; UK, United Kingdom; US, United States; Vi-CRM₁₉₇, Vi-non-toxic variant of diphtheria toxin; Vi-DT, Vi-diphtheria toxoid; Vi-rEPA, Vi-*Pseudomonas aeruginosa* exoprotein A; Vi-TT, Vi-tetanus toxoid.

^aThis vaccine went through a full clinical development program but is not licensed.

^bThis trial had a small sample size, with <100 children aged <2 years of age receiving TCV; therefore, any firm conclusions are unable to be drawn from it.

introduction into endemic countries is stronger. The development and use of CHIMs to accelerate the testing of vaccines has, as with other pathogens, proven to be a valuable addition to large-scale field trials. With the availability and funding of efficacious typhoid vaccines and the continued development of vaccines for paratyphoid, the global control of enteric fever could now be significantly strengthened.

Notes

Financial support. This work was supported by the Bill & Melinda Gates Foundation (grant numbers OPP1116967 and OPP1151153) and the Wellcome Trust (strategic award 106158/Z/14/Z).

Supplement sponsorship. This supplement has been funded by the New Venture Fund.

Potential conflicts of interest. A. J. P. is Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation and the European Medicines Agency scientific advisory group on vaccines and is a member of the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization. A. J. P. reports funding from the National Institute for Health Research Oxford Biomedical Research Centre. V. E. P. has received reimbursement from Merck for travel expenses unrelated to the subject of this manuscript and is a member of the WHO Immunization and Vaccine-Related Implementation Research Advisory Committee. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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