Typhoid in Africa and vaccine deployment

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Typhoid, one of the classic infectious diseases afflicting humanity, is still a relatively common illness in many lower-income and middle-income countries (LMIC).[1] The disease is associated with chronic fever that, if not treated, can lead to complications such as intestinal perforation or neurological problems.[2] The diagnosis of typhoid is complicated because clinical presentation can be non-specific and can resemble a number of other diseases, such as malaria, typhus, and various viral infections. The current typhoid diagnostic kits are relatively unreliable, and microbial culture from blood or other bodily secretions of the main bacterial aetiological agents *Salmonella enterica* serotype Typhi and *S enterica* serotype Paratyphi A remains the gold standard.[3] Microbial culture requires the availability of adequate laboratory facilities, including blood and microbial culture equipment, and appropriate bacteriological expertise. Unfortunately, these are not always present in LMIC settings and the incidence of typhoid in many regions, particularly Africa, remains relatively undefined. Nevertheless, more than 20 million cases of typhoid have been estimated globally, most of which are caused by *S* Typhi, with between 200 000 and 600 000 deaths.[1] However, the estimates are compromised by limited epidemiological information and restricted geographical coverage, as well as the problems with diagnosis.

Interest in typhoid has increased in recent years, driven by a number of factors. Multidrug resistance has been increasingly reported as a characteristic of *S* Typhi isolated in the past decade and from different parts of the globe.[4] Although there is historical evidence that typhoid has been established in south and southeast Asia for decades, there have been increasing reports of typhoid in different African countries, potentially associated with multidrug resistance.[5] Furthermore, a particular haplotype of *S* Typhi, known as H58 or 4.3.1, has been linked to the spread of multidrug resistance, and this strain might be driving typhoid into new geographical areas where typhoid was previously absent or under reported.[6] Multidrug resistant *S* Typhi respond more slowly to antibiotic treatment,[7] and such strains might be stimulating an increased use of antibiotics (and indirectly promoting multidrug resistance) in the community, where antibiotics are freely available without prescription. Additionally, a new generation of typhoid vaccines, based on conjugate technology and the Vi capsular antigen of *S* Typhi, are being developed and have been licenced in some countries.[8]

In response to the lack of epidemiological information on typhoid in Africa, the Typhoid Fever Surveillance in Africa Programme (TSAP), funded by the Bill & Melinda Gates Foundation and covering ten countries and 13 sites across Africa, was established between 2010 and 2014. In this issue of *The Lancet Global Health*, Florian Marks and colleagues[9] present the results of a multicentre population-based surveillance study implemented by TSAP that uses standardised approaches based around blood culture, to provide an estimate of typhoid disease burden. *S* Typhi, together with isolates of other non-typhoidal *Salmonella* serovars (eg, Typhimurium, Enteritidis, Dublin) were the most common bacteria found in the blood at many of the sites, outstripping *Streptococcus pneumoniae* and *Escherichia coli*. A large variation existed in the adjusted incidence rates (AIR) of *S* Typhi between the different sites, with no isolates at all in Sudan and Ethiopia but with estimated levels of 383 per 100 000 at one site in Burkina Faso. Typhoid was found in both young infants and in school age children, with higher AIR in children younger than 15 years old. Thus, the incidence of typhoid varied significantly between the sites, suggesting that the epidemiology is complex and potentially a highly variable patchwork exists across the region. Worryingly, significant levels of multidrug resistance were found in *S* Typhi and in non-typhoidal *Salmonella* at some of the sites. The establishment of these linked sites across Africa has the added bonus of providing an infrastructure for further studies on typhoid, but this system can also be potentially exploited for other studies on infectious diseases, antimicrobial resistance, or even non-communicable diseases. For example, the epidemiology of many of the non-*Salmonella* bacteria isolated in the study (eg, Klebsiella) is poorly understood in the region.

These data indicate that typhoid is a substantial disease burden in many parts of Africa, with the incidence levels likely to be an underestimate because of the difficulty of estimating true levels on the basis of microbial culture. The report has encouraged the funding of TSAP to be continued for a further 2 years to gather more information, and these data, together

with information from other sites, have prompted further funding into typhoid vaccine development and deployment. A key challenge is to determine how useful an efficacious vaccine might be in LMICs, where the levels of disease vary so greatly between different regions. Such studies might be pivotal to facilitate the deployment of such vaccines. In this regard, a need exists to develop economic models that provide governments and agencies with information that will inform decision making. The changing epidemiological pattern, the emergence of a potentially more aggressive multidrug resistant clade, and the likelihood of increased antibiotic usage in communities affected by the disease are creating a sense of urgency. Indeed, typhoid might prove to be a useful model of how to measure any benefit of vaccination on controlling the indiscriminate use of antibiotics. Other areas of interest will be the development of better diagnostics for the disease and the provision of proof that typhoid conjugate vaccines are as efficacious in different settings as the single efficacy study performed to date suggested.[10]

Gordon Dougan
The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SA, UK and Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
gd1@sanger.ac.uk

I declare no competing interests.

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