



## The global burden of enteric fevers in the age of typhoid-conjugate vaccines

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In *The Lancet Infectious Diseases*, authors led by the Institute of Health Metrics and Evaluation (University of Washington, Seattle, WA, USA) add to our understanding of enteric fevers by presenting a comprehensive and systematic analysis of the global burden of typhoid and paratyphoid fevers using data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017.<sup>1</sup> Unlike previous estimates, the investigators explore the global, regional, and country burden of enteric diseases and estimate age-specific mortality and case-fatality rates by region and age.

The authors estimated 10.9 million (95% uncertainty interval [UI] 9.3–12.6) cases of typhoid fever and 116.8 thousand (65.4–187.7) deaths due to *Salmonella enterica* serovar Typhi in 2017. Years of life lost (YLLs) attributed to typhoid fever were 8.3 million (95% UI 4.6–13.4) and disability-adjusted life-years (DALYs) were 8.4 million (4.7–13.6). These results correspond to an estimated 53.6% reduction in cases and 57.8% reduction in deaths since 1990. Wisely, the authors also present data for paratyphoid fever. The paratyphoid fever burden is substantially lower than that of typhoid fever: an estimated 3.4 million (2.7–4.2) cases and 19.1 thousand (8.7–37.3) deaths occurred from paratyphoid fever in 2017. YLLs attributed to paratyphoid fever in 2017 were 1.4 million (0.6–2.6) and DALYs were 1.4 million (0.6–2.6). Between 1990 and 2017, the authors estimate a 61.7% reduction in cases of paratyphoid fever and a 67.0% reduction in deaths.

Although the estimates presented in this study reflect substantial gains in prevention and treatment over several decades, enteric fevers continue to undermine the health and economic wellbeing of resource-poor families and generate substantial costs to health services in endemic countries.<sup>2,3</sup> A report of extensively-drug resistant *S Typhi* from Pakistan has amplified the warning that effective treatment is becoming increasingly challenging and could reverse recent progress.<sup>4</sup> Fortunately, for prevention of *S Typhi*, in January, 2018, WHO prequalified a conjugate vaccine, Typbar-TCV (Bharat Biotech, Hyderabad, India), in which the Vi polysaccharide capsule antigens are

linked to tetanus toxoid (Vi-TT). In a human challenge trial involving a wild strain of *S Typhi*, Vi-TT showed up to 87% efficacy depending on clinical endpoints.<sup>5</sup> Typbar-TCV can be administered to adults, children, and infants as young as 6 months and, based on efficacy observed with a previous conjugate vaccine, is thought to be effective for at least 5 years.<sup>6</sup> Gavi, the Vaccine Alliance, has announced US\$85 million in funding for eligible countries to introduce typhoid conjugate vaccines in 2019 and 2020.<sup>7</sup>

With funding approved for vaccine adoption in many endemic countries, the results of this study will assist donors, international and regional agencies, and national governments to develop and fund rational vaccination strategies. Still, as the authors note, data gaps remain in many countries and regions (eg, sub-Saharan Africa). These data gaps will need to be closed through population-based surveillance to clarify the need for, and monitor the progress of, typhoid conjugate vaccines. The authors' results also imply a substantial burden from paratyphoid fever, providing support for development of a *S Paratyphi* vaccine. No such vaccine is available at present. Given the future use of *S Typhi* conjugate vaccines and the need to monitor the global burden of *S Typhi* alone, authors could consider, in future publications, providing all results separated by causative pathogen rather than combining results (eg, typhoid plus paratyphoid age-standardised incidence rates).

Expanded data on the global, regional, and national burden of enteric fever as provided in this report, and the advent of a WHO-prequalified conjugate vaccine are advancing the control of enteric fevers and will improve the health and wellbeing of resource-poor families in endemic countries.

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We declare no competing interests.

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- 1 GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis* 2019; published online Feb 18. [http://dx.doi.org/10.1016/S1473-3099\(18\)30685-6](http://dx.doi.org/10.1016/S1473-3099(18)30685-6).
- 2 Riewpaiboon A, Piatti M, Ley B, et al. Cost of illness due to typhoid fever in Pemba, Zanzibar, East Africa. *J Health Popul Nutr* 2014; **32**: 377–85.
- 3 Poulos C, Riewpaiboon A, Stewart JF, et al. Cost of illness due to typhoid fever in five Asian countries. *Trop Med Int Health* 2011; **16**: 314–23.
- 4 Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an extensively drug-resistant *Salmonella enterica* serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *MBio* 2018; **9**: e00105-18.
- 5 Jin C, Gibani MM, Moore M, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella* Typhi: a randomised controlled, phase 2b trial. *Lancet* 2017; **390**: 2472–80.
- 6 Lin FY, Ho VA, Khiem HB, et al. The efficacy of a *Salmonella* typhi Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001; **344**: 1263–69.
- 7 Gavi—The Vaccine Alliance. New typhoid vaccine to receive Gavi support. April 3, 2018. <https://www.gavi.org/library/news/statements/2018/new-typhoid-vaccine-to-receive-gavi-support/> (accessed Dec 3, 2018).

## Antibiotic prescription in paediatric emergency departments: fear and reason



In their cross-sectional study of 5177 children admitted to 28 emergency departments across Europe between Nov 1, 2014, and Feb 28, 2016, Josephine van de Maat and colleagues<sup>1</sup> report in *The Lancet Infectious Diseases* that 1454 (32%) of 4560 children without comorbidities were given a course of antibiotics on discharge. The variation in prescription frequency across countries was vast, from 19% (81 of 428 children received antibiotics) in Switzerland to 64% (450 of 708) in Turkey. The authors focused their analysis on respiratory tract infections, which accounted for 82% of all antibiotic prescriptions, to identify factors affecting prescription decisions. Duration of fever, elevated C-reactive protein concentration, focal abnormalities, or, to a lesser degree, diffuse abnormalities in chest X-rays were associated with increased prescribing but these factors did not fully explain the variance in the model. The authors hypothesised that other factors they did not include might be contributing. However, the high frequency of prescriptions also raises the issue of irrationality toward prescribing antibiotics.

Why do we prescribe antibiotics? To avoid death can be one reason. Serious bacterial infections are rare but potentially life-threatening and suboptimal care (eg, late recognition or delayed antibiotic treatment) could lead to death.<sup>2</sup> When in doubt, clinicians generally might prescribe antibiotics, thinking that the treatment would be less harmful than missing a severe bacterial infection. Pneumonia is a good example of a doubtful situation that could explain why children with lower respiratory tract infections showed the most variation in antibiotic prescription frequency.<sup>1</sup> In fact, there is no international consensus on diagnostic criteria for bacterial pneumonia, one of the leading global causes of death, for which

*Streptococcus pneumoniae* was implicated by the *Lancet* Infectious Diseases Global Burden of Disease 2016 study on lower respiratory infections.<sup>3</sup> In this report, estimated mortality due to pneumonia in children under 5 years of age was fewer than two in 1000 in western European countries, which meant that about 250 000 children needed to be treated with antibiotics to avoid one death. These proportions were 12.4/1000 children in Turkey and 50.8/1000 in Romania, which meant that the number to treat to prevent one death was considerably lower (about 7000). The high frequency of antibiotic prescriptions for lower respiratory tract infections could thus reflect fear of death, as observed for Turkey, but in other centres the frequency was higher than expected despite a low mortality rate within the country. Moreover, in the investigators' multilevel analysis of determinants of antibiotic prescription, individual factors such as signs usually associated with severe bacterial infection did not appear to influence the prescription frequency, whereas radiological signs, with arguable diagnostic value, had a significant effect. This observation supports the hypothesis that some antibiotic prescriptions are driven by sepsis phobia and the trivialisation of antibiotics, rather than by clinical evidence.

In high-income countries, implementation of pneumococcal vaccination has reduced the incidence of pneumonia and contributed more to a reduction in mortality than antibiotic use.<sup>3,4</sup> In these settings, patients with lower respiratory tract infections are at a decreased risk of death and severe bacterial infections compared with those in other lower-income European countries, which tend to overprescribe antibiotics. The US<sup>5</sup> and UK<sup>6</sup> guidelines on treating pneumonia in children, which

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