

Progress in Typhoid Fever Epidemiology

John A. Crump

Centre for International Health, University of Otago, Dunedin, New Zealand

Salmonella enterica subspecies *enterica* serovar Typhi (*Salmonella* Typhi) is the cause of typhoid fever and a human host–restricted organism. Our understanding of the global burden of typhoid fever has improved in recent decades, with both an increase in the number and geographic representation of high-quality typhoid fever incidence studies, and greater sophistication of modeling approaches. The 2017 World Health Organization Strategic Advisory Group of Experts on Immunization recommendation for the introduction of typhoid conjugate vaccines for infants and children aged >6 months in typhoid-endemic countries is likely to require further improvements in our understanding of typhoid burden at the global and national levels. Furthermore, the recognition of the critical and synergistic role of water and sanitation improvements in concert with vaccine introduction emphasize the importance of improving our understanding of the sources, patterns, and modes of transmission of *Salmonella* Typhi in diverse settings.

Keywords. epidemiology; death; incidence; typhoid fever; *Salmonella*.

Salmonella enterica subspecies *enterica* serovar Typhi (*Salmonella* Typhi) is the cause of typhoid fever. Together, *Salmonella* Typhi and *Salmonella* serovar Paratyphi A are the major agents of enteric fever. Like other typhoidal *Salmonella* serovars, *Salmonella* Typhi is a human host–restricted organism. The role of water as a vehicle for typhoid fever has been appreciated since the late 1800s [1, 2] and the role of food not long after [3]. Our understanding of the global burden of typhoid fever has improved in recent decades, with an increase in both the number and geographic representation of high-quality typhoid fever incidence studies, and greater sophistication of modeling approaches. The 2017 World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) recommendation for the introduction of typhoid conjugate vaccines (TCVs) for infants and children aged >6 months in typhoid-endemic countries [4] is likely to require further improvements in our understanding of typhoid burden not only at the global level, but also at the national and subnational levels. Furthermore, the recognition of the critical and synergistic role of water and sanitation improvements in concert with vaccine introduction [5] emphasizes the need to improve our understanding of the sources, patterns, and modes of transmission of *Salmonella* Typhi in diverse local settings. This manuscript summarizes current knowledge, areas of progress, and future directions for work in these areas of *Salmonella* Typhi epidemiology.

CHAIN OF INFECTION

Reservoir

Humans are the reservoir (defined as the habitat in which the agent normally lives, grows, and multiplies) of *Salmonella* Typhi. *Salmonella* Typhi has limited capacity to multiply outside of the human host, but it may survive for extended periods in the environment [6]. Acute *Salmonella* Typhi infection presents as typhoid fever. Typhoid fever may be difficult to distinguish clinically from other febrile illnesses. If untreated, intestinal, neuropsychiatric, and other complications develop in some patients. However, acute infection can also be mild and self-limited. Human challenge studies demonstrate that fecal shedding and even bacteremia may occur in the absence of clinical signs of typhoid fever [7].

Portal of Exit, Route of Infection, and Source

Feces represent the major portal of exit of *Salmonella* Typhi, although shedding in urine has also been documented [8]. *Salmonella* Typhi may be shed in the stool or urine during and following both clinical and subclinical acute infection. Shedding may be temporary or chronic. Temporary shedding may be acute or convalescent. A convalescent carrier sheds *Salmonella* Typhi for ≥ 3 –12 months after the onset of acute illness. A chronic carrier sheds typhoid bacilli for >12 months after onset of acute illness. Practically speaking, a chronic carrier may be defined as someone with no history of typhoid fever or someone who had the disease >1 year previously, who has fecal or urine cultures positive for *Salmonella* Typhi separated by at least 48 hours. The relative contribution of temporary shedding versus shedding from chronic carriers to new infections remains an unanswered yet critical question for typhoid control and elimination. Chronic carriers are known to be a major source of domestically acquired *Salmonella* Typhi infections in countries with low typhoid incidence [9]. However, “Typhoid Mary” [3] has assumed a place in both popular and medical

Presented in part: 10th International Conference on Typhoid and Other Invasive Salmonellosis, Kampala, Uganda, 4–6 April 2017.

Correspondence: J. A. Crump, Otago Global Health Institute, University of Otago, PO Box 56, Dunedin 9054, New Zealand (john.crump@otago.ac.nz).

Clinical Infectious Diseases® 2019;68(S1):S4–9

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited. DOI: 10.1093/cid/ciy846

consciousness that belies the potentially greater contribution to transmission of temporary shedding in settings of high typhoid incidence. *Salmonella* Typhi transmission is by the fecal–oral route. Water and food contaminated by human feces are the major sources (defined as the places from which the agent is transferred to a host) of *Salmonella* Typhi. The human reservoir is considered to occasionally be the source of *Salmonella* Typhi, and ingestion of human feces during oral–anal sex has been implicated [10].

Mode and Patterns of Transmission

The mode of *Salmonella* Typhi transmission is considered to be largely indirect and predominantly vehicle-borne through contaminated water or food [11]. Water and food usually serve as passive vehicles for *Salmonella* Typhi. While *Salmonella* Typhi may survive for extended periods on vehicles, multiplication of *Salmonella* Typhi in water and food is uncommon [6]. Some group *Salmonella* Typhi transmission into 2 broad patterns. In short-cycle transmission, food and water are contaminated by fecal shedding in the immediate environment, and transmission is mediated through inadequate hygiene and sanitation measures. In long-cycle transmission there is contamination of the broader environment, such as pollution of untreated water supplies by human feces and use of raw human feces or untreated sewage as a crop fertilizer [12]. Epidemiologic investigations underscore the important role of chronic carriers in short-cycle foodborne typhoid outbreaks in countries with low typhoid incidence [9], and the potentially large scale of long-cycle waterborne transmission in many high-incidence settings [13]. The means by which the source is contaminated and type of vehicles involved vary considerably from location to location, underscoring the importance of local epidemiologic investigations for informing nonvaccine control measures.

Portal of Entry and Host

The portal of entry for *Salmonella* Typhi infection is the mouth, usually through ingestion of fecally contaminated water or food. Infection occurs in a susceptible human host. The incubation period shortens and the risk for infection and disease increases with the ingested dose [14]. Gastric acid provides an important barrier to *Salmonella* Typhi accessing the small intestinal mucosa and, in turn, the reticuloendothelial system. Natural and vaccine-induced immunity provide partial protection against typhoid fever [15].

BURDEN OF DISEASE

Burden of disease represents the impact of a health problem, and is often expressed as disability-adjusted life-years (DALYs). DALYs are calculated by adding years of life lost (YLL) from dying early to years lost due to disability (YLD). The YLL is calculated by multiplying the number of deaths due to a condition by the standard life expectancy at the age of death. YLD

is determined by multiplying disease incidence, by the disease's disability weight, and the duration of illness until remission or death [16]. Unlike diarrhea and pneumonia where a syndrome-wide “envelope” of DALYs is established and then attributed to specific causes, there is presently no DALY envelope for febrile illness. Consequently, a “natural history approach” is taken to estimate the burden of febrile illnesses such as typhoid fever. Here, pathogen-specific studies of disease incidence, complications, and deaths are sought to develop estimates of burden [17]. A summary of typhoid fever burden of disease-related studies from 1980 through 2016 is provided in Table 1.

Incidence

The incidence of a disease is the number of new cases per population per unit time. For typhoid fever, incidence is usually expressed as cases per 100 000 population per year. Typhoid fever incidence is often classified as low, medium, high [35], and, more recently, very high [31], corresponding to incidence bands of <10, 10–100, >100–<500, and ≥500 per 100 000 per year, respectively. For burden of disease calculations, population-based incidence measured by active disease surveillance accounting for blood culture insensitivity is used [35]. Studies combining sentinel healthcare facility surveillance with healthcare utilization surveys to account for underascertainment are increasingly done to approximate population-based disease incidence with lower resource investment [17, 36].

Early attempts to estimate the global burden of typhoid fever were hampered by the very limited number of contemporary population-based studies of typhoid fever incidence using blood culture confirmation from typhoid-endemic areas [18, 19]. Data from the control arm of the burgeoning number of typhoid vaccine trials were central to the 2000 estimate of global typhoid incidence, but their use was tempered by concern for bias due to the preference for conducting vaccine trials in high-incidence settings [35]. Since that time, a number of studies [37–39] have been completed that bolster data on typhoid fever incidence from an increasingly diverse range of locations. Such studies include those that are truly population-based, with household surveillance for fever and blood culture in the home or by active referral to healthcare facilities [37]. In addition, a number of recent incidence studies rely on healthcare facility-based surveillance supplemented with healthcare utilization surveys that provide multipliers to account for underascertainment related to healthcare access among febrile persons [39].

There is growing recognition of the considerable variation in typhoid fever incidence that may occur in place and over time. Whereas in 2000 typhoid fever appeared to be less common or underascertained in Africa compared with Asia [35, 40], more recent studies confirm that typhoid fever incidence is high in some parts of Africa [37, 39]. Furthermore, typhoid has been demonstrated to occur at high incidence after years of little disease in some locations [41] while declining markedly from high

Table 1. Global Estimates of Typhoid Fever Incidence, Disability, and Death, 1980–2016

Origin (referencel(s)) Coverage	Year												
	1980	1996	2000	2010	2010	2010	2010	2010	2010	2013	2015	2015	2016
WHO [18] Global, except China	12.5	16.0	21.7	20.6	26.9	21.0	21.0	11.0	11.0	11.0	12.5	178	11.8
WHO [19] Global	(17.5–24.2)	(18.3–35.7)	(78–44.9)	(9.6–14.4)	(9.6–14.4)	(9.6–14.4)	(9.6–14.4)	(10.9–14.3)	(6.9–48.4)	(10.2–13.6)
WHO [20] LMIC, unadjusted ^a	10 292	11 128	11 128	11 128	11 128	10 576	...	8843
JHU [21] Global	(3805–22 028)	(6014–18 315)	(6014–18 315)	(6014–18 315)	(6014–18 315)	(5896–17 598)	...	(4902–14 436)
CDC [35] Global	(53 519–309 903)	(23 800–359 100)	(23 800–359 100)	(23 800–359 100)	(23 800–359 100)	148 800	...	128 200
IHME [23, 24] Global, including paratyphoid	148 800	...	(70 100–210 200)
IHME [25–27] Global	148 800
IHME [28–30] Global	148 800
Yale [31] LMIC	148 800
IHME [32–34] Global	148 800

Abbreviations: CDC, US Centers for Disease Control and Prevention; CI, confidence interval or credible interval; DALY, disability-adjusted life-years; IHME, Institute for Health Metrics and Evaluation; IVI, International Vaccine Institute; JHU, Johns Hopkins University; LMIC, low-to middle-income country; UI, uncertainty interval; WHO, World Health Organization.

^aThe authors estimated the number of typhoid fever cases in LMICs in 2010 after adjusting for water-related risk was 11.9 million (95% confidence interval [CI], 9.9–14.7 million) cases with 129 000 (95% CI, 75 000–208 000) deaths.

incidence levels elsewhere [39]. Furthermore, *Salmonella* serovars other than Typhi play differing roles by location. Among Asian bloodstream infection studies, both typhoid fever and paratyphoid fever are common [42]. African studies demonstrate that nontyphoidal *Salmonella* invasive disease is often as common or exceeds typhoid fever incidence in some locations [43]. Estimates from the past 5 years indicate that 11.0–17.8 million typhoid fever illnesses occur annually worldwide (Table 1). Notwithstanding substantial improvements and changes in the amount of source data and methods for extrapolation, the annual number of typhoid fever illnesses have not kept pace with global population growth. However, typhoid fever still ranks high among the major causes of infectious disease illness and death [32, 33].

Drivers of Typhoid Fever Incidence

Perhaps not surprisingly, given predominant modes of *Salmonella* Typhi transmission, early 20th century data from large cities in Europe and North America repeatedly demonstrated a reduction in typhoid fever illnesses and deaths ecologically associated with measures to improve the microbiologic quality of drinking water [2]. It is likely that similar health gains could be achieved in typhoid-endemic countries if human feces could reliably be excluded from drinking water and food. In 1990, the regions of sub-Saharan Africa, South and Southeast Asia, and Oceania had the lowest population coverage with improved water and sanitation facilities. By 2015, water and sanitation coverage had increased markedly in South and Southeast Asia, and less so in sub-Saharan Africa [44]. However, during the same period Oceania made little progress in either category and is now thought to experience the highest incidence of typhoid fever of any global region [31].

Disability and Death

The case fatality risk of typhoid fever was approximately 10%–30% in the preantimicrobial era [45]. With effective antimicrobials, the case fatality risk is usually <1%. Antimicrobial-resistant *Salmonella* Typhi is a major global health concern [46]. Clinical studies demonstrate the association between antimicrobial resistance and poor patient outcomes [47]. One of the most important modifiable contributors to a poor outcome in typhoid fever is a delay in instituting effective antimicrobial treatment. This delay is more likely to occur where typhoid fever is underrecognized as a cause of febrile illness [48], and where empiric antimicrobial therapy does not correspond with patterns of antimicrobial susceptibility of local *Salmonella* Typhi strains.

Population-based studies of typhoid fever incidence are rarely large enough to accurately estimate the prevalence of complications such as intestinal perforation and deaths. The early detection and enhanced clinical management of typhoid fever inherent and appropriate in such studies modifies the

occurrence of complications and deaths. Hospital-based studies are likely to be biased toward more severe disease or those with the ability to access hospital-level healthcare [36]. To date, estimates of the proportion of typhoid fever patients developing complications and dying has been based on expert opinion and on systematic reviews of hospital-based studies that have inherent limitations. Research under way at present is anticipated to shore up estimates of typhoid fever complications and deaths.

Extrapolation, Uncertainty, and Data Gaps

The sophistication of approaches to extrapolating typhoid fever incidence from locations with robust studies to other geographic areas has increased over time. Early efforts used geographic proximity as the basis of extrapolation [35], an approach that may be extended to account for socioeconomic conditions. Subsequently, water-related risk factors for typhoid fever have been used as a basis for extrapolation [20]. More recently, a range of national or subnational characteristics that are not necessarily on the causal pathway for typhoid fever have been used to inform models for extrapolation [31, 49].

Limited incidence data, variation in the quality of incidence studies, and extrapolation introduce considerable uncertainty into global typhoid fever burden estimates. Uncertainty was not formally addressed in early typhoid fever estimates, but is explored by sensitivity analysis or is represented with uncertainty intervals in contemporary efforts (Table 1).

There remain many data gaps related to typhoid fever burden estimation [50]. Key areas where more data are needed include wider geographic representation of typhoid incidence studies, research on typhoid complications and deaths, and a better understanding of typhoid fever incidence and severity among infants and young children.

Typhoid Fever Among Infants and Young Children

A recent systematic review of pediatric enteric fever showed that typhoid fever is common among children <5 years of age in many locations [51]. However, the review also highlighted the lack of detailed data on typhoid occurrence in the youngest age groups, especially those <2 years of age. Figure 1 illustrates potential

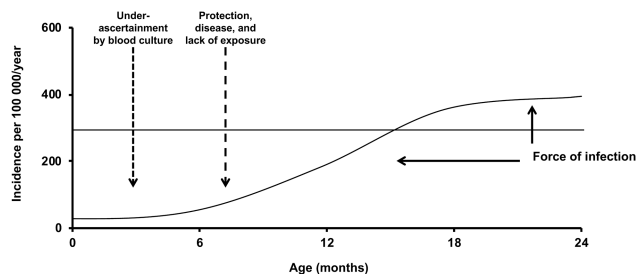


Figure 1. Schematic representation of potential drivers of typhoid fever incidence and uncertainty about typhoid fever incidence among infants and young children <2 years of age.

drivers of typhoid fever incidence and uncertainty about typhoid fever incidence among infants and young children <2 years of age. Typhoid fever incidence likely describes a sigmoid curve in this age group, with low incidence in the neonatal period, rising with age. The main drivers of relatively low typhoid incidence among neonates and infants include potential protection from maternal antibodies, the somewhat controversial possibility of less severe disease in younger age groups, and lack of exposure to fecally contaminated water and food vehicles during the period of exclusive or predominant breastfeeding. Force of infection, as measured by population typhoid fever incidence, will have the effect of pushing the peak of disease incidence toward younger age groups and the magnitude of incidence upward [35]. However, typhoid fever may be underascertained in younger age groups through underuse of blood culture in neonates and infants, and inadequate blood volumes for culture and the higher risk for blood culture contamination in the young, when it is attempted (Figure 1).

A growing body of evidence demonstrates a substantial typhoid fever problem among infants and children in settings of high typhoid fever incidence [41]. With TCVs able to protect infants and young children, WHO SAGE recently recommended the use of TCV among those aged >6 months in typhoid-endemic countries [4]. Data on typhoid fever occurrence among infants and young children, as well as other age groups, will be invaluable as countries strive to make evidence-based decisions about whether and at what age to introduce TCVs.

THE WAY FORWARD

Despite >100 years of research, important gaps remain in our understanding of typhoid fever epidemiology. More data are needed on the contribution of temporary versus chronic carriers to *Salmonella* Typhi transmission, particularly in the low-resource areas where typhoid fever is particularly common. Understanding the proportion of typhoid fever infections that are subclinical and their role, if any, in transmission as well as the efficacy of available typhoid vaccines in preventing shedding is important to designing effective strategies to interrupt transmission. It is apparent that patterns and modes of transmission of *Salmonella* Typhi vary considerably from place to place. Identifying and tracking the relative contributions of short-cycle and long-cycle patterns of transmission, and the relative contributions of water, food vehicles, and other sources to transmission will be central to control strategies in a given location. Presumably reflecting both the remaining uncertainties and the variations in typhoid epidemiology, experts differ in their opinions on the role of different exposure pathways for *Salmonella* Typhi infection by region [52]. At the same time, understanding which components of water, sanitation, and hygiene interventions are most appropriate for preventing typhoid fever in particular locations and globally are highly dependent on such knowledge.

An “envelope” of DALYs for fever without localizing features, modeled on the approach for diarrhea and pneumonia, or other innovations such as the application of serologic surveys to support burden estimation [53] await development and refinement. Consequently, the typhoid fever community must rely on a “natural history” approach to estimating and monitoring the global burden of typhoid fever. Natural history models of typhoid fever are only as good as the quality and representativeness of contributing studies of incidence, complications, and deaths, and the performance of models for data extrapolation. Although the number of incidence studies and the sophistication of modeling have grown, major data gaps remain. In particular, incidence studies are lacking for large geographic areas and among infants and young children. Furthermore, our understanding of the occurrence of complications and deaths and the contribution of antimicrobial resistance to these would benefit from more research. The recent WHO SAGE recommendation for the introduction of TCVs for infants and children aged >6 months in typhoid-endemic countries [4] is likely to increase the demand for such data in many countries seeking to make vaccine decisions. The growing recognition of the considerable variation in the occurrence of typhoid fever in both place [20, 35] and time [41], as well as the anticipated need to measure vaccine impact in countries that introduce TCV, underscores the importance of robust long-term, multiyear typhoid fever surveillance. Ideally, such surveillance should be integrated with surveillance for other major febrile illnesses hitherto overlooked or monitored with independent vertical surveillance programs [48].

Notes

Acknowledgments. The author thanks Dr Eric D. Mintz, MD, MPH, and Dr Christian S. Marchello, PhD, for comments and suggestions.

Financial support. This work was supported by the Bill & Melinda Gates Foundation (grant numbers OPP1125993 and OPP1158210). J. A. C. is supported by the joint US National Institutes of Health (NIH)/US National Science Foundation Ecology and Evolution of Infectious Disease program (grant number R01 TW009237); the NIH (grant number R01AI121378); the UK Biotechnology and Biological Sciences Research Council (BBSRC) (grant number BB/J010367/1); the UK BBSRC Zoonoses in Emerging Livestock Systems program (award numbers BB/L017679, BB/L018926, and BB/L018845); and the New Zealand Health Research Council through the e-ASIA Joint Research Programme (award number 16/697).

Supplement sponsorship. This supplement was sponsored by Coalition against Typhoid, Sabin Vaccine Institute, Bill & Melinda Gates Foundation.

Potential conflicts of interest. Author certifies no potential conflicts of interest. The author has 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.

References

- Budd W. Typhoid fever, its nature, mode of spreading and prevention. London: Longmans Green and Co, 1873.
- Sedgwick WT, MacNutt JS. On the Mills-Reincke phenomenon and Hazen's theorem concerning the decrease in mortality from diseases other than typhoid fever following the purification of public water supplies. *J Infect Dis* 1910; 7:490–564.
- Soper GA. The work of a chronic typhoid germ distributor. *JAMA* 1907; 48:2019–22.
- World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2017—conclusions and recommendations. *Wkly Epidemiol Rec* 2017; 92:729–47.
- Pitzer VE, Bowles CC, Baker S, et al. Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: a mathematical modeling study. *PLoS Negl Trop Dis* 2014; 8:e2642.
- Mitscherlich E, Marth EH. 1. Special part: bacteria considered in alphabetical order. In: Mitscherlich E, Marth EH, eds. *Microbial survival in the environment*. Berlin, Heidelberg, New York, Tokyo: Springer, 1984:1–560.
- Waddington CS, Darton TC, Jones C, et al. An outpatient, ambulant-design, controlled human infection model using escalating doses of *Salmonella* Typhi challenge delivered in sodium bicarbonate solution. *Clin Infect Dis* 2014; 58:1230–40.
- Sears HJ, Garhart RW, Mack DW. A milk borne epidemic of typhoid fever traced to a urinary carrier. *Am J Public Health (N Y)* 1924; 14:848–54.
- Olsen SJ, Bleasdale SC, Magnano AR, et al. Outbreaks of typhoid fever in the United States, 1960–1999. *Epidemiol Infect* 2003; 130:13–21.
- Roller ME, Olsen SJ, Kressel AB, et al. Sexual transmission of typhoid fever: a multistate outbreak among men who have sex with men. *Clin Infect Dis* 2003; 37:141–4.
- Luby SP, Faizan MK, Fisher-Hoch SP, et al. Risk factors for typhoid fever in an endemic setting, Karachi, Pakistan. *Epidemiol Infect* 1998; 120:129–38.
- González-Guzmán J. An epidemiological model for direct and indirect transmission of typhoid fever. *Math Biosci* 1989; 96:33–46.
- Mermin JH, Villar R, Carpenter J, et al. A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. *J Infect Dis* 1999; 179:1416–22.
- Hornick RB, Greisman SE, Woodward TE, DuPont HL, Dawkins AT, Snyder MJ. Typhoid fever: pathogenesis and immunologic control. *N Engl J Med* 1970; 283:686–91.
- Wain J, Hien TT, Connerton P, et al. Molecular typing of multiple-antibiotic-resistant *Salmonella enterica* serovar Typhi from Vietnam: application to acute and relapse cases of typhoid fever. *J Clin Microbiol* 1999; 37:2466–72.
- Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bull World Health Organ* 1994; 72:429–45.
- Crump JA, Kirk MD. Estimating the burden of febrile illnesses. *PLoS Negl Trop Dis* 2015; 9:e0004040.
- Edelman R, Levine MM. Summary of an international workshop on typhoid fever. *Rev Infect Dis* 1986; 8:329–49.
- World Health Organization. *The world health report 1996: fighting disease, fostering development*. Geneva, Switzerland: WHO, 1996.
- Mogasale V, Maskery B, Ochiai RL, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *Lancet Glob Health* 2014; 2:e570–80.
- Buckle GC, Walker CL, Black RE. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. *J Glob Health* 2012; 2:10401.
- Kirk MD, Pires SM, Black RE, et al. World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal and viral diseases, 2010: a data synthesis. *PLoS Med* 2015; 12:e1001921.
- Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380:2197–223.
- Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380:2095–128.
- GBD 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386:743–800.
- GBD 2013 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet* 2015; 386:2145–91.
- GBD 2013 Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 385:117–71.
- GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388:1545–602.
- GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388:1603–58.

30. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**; 388:1459–544.
31. Antillón M, Warren JL, Crawford FW, et al. The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. *PLoS Negl Trop Dis* **2017**; 11:e0005376.
32. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **2017**; 390:1211–59.
33. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **2017**; 390:1151–210.
34. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **2017**; 390:1260–344.
35. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* **2004**; 82:346–53.
36. Crump JA, Youssef FG, Luby SP, et al. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. *Emerg Infect Dis* **2003**; 9:539–44.
37. Breiman RF, Cosmas L, Njuguna H, et al. Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa. *PLoS One* **2012**; 7:e29119.
38. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al; Domi Typhoid Study Group. A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bull World Health Organ* **2008**; 86:260–8.
39. Marks F, von Kalckreuth V, Aaby P, et al. Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. *Lancet Glob Health* **2017**; 5:e310–23.
40. Mweu E, English M. Typhoid fever in children in Africa. *Trop Med Int Health* **2008**; 13:1–9.
41. Feasey NA, Masesa C, Jassi C, et al. Three epidemics of invasive multidrug-resistant *Salmonella* bloodstream infection in Blantyre, Malawi, 1998–2014. *Clin Infect Dis* **2015**; 61(Suppl 4):S363–71.
42. Deen J, von Seidlein L, Andersen F, Elle N, White NJ, Lubell Y. Community-acquired bacterial bloodstream infections in developing countries in south and southeast Asia: a systematic review. *Lancet Infect Dis* **2012**; 12:480–7.
43. Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infect Dis* **2010**; 10:417–32.
44. World Health Organization/United Nations Children's Fund. Progress on sanitation and drinking water: 2015 update and MDG assessment. Geneva, Switzerland: WHO, **2015**.
45. Butler T, Knight J, Nath SK, Speelman P, Roy SK, Azad MA. Typhoid fever complicated by intestinal perforation: a persisting fatal disease requiring surgical management. *Rev Infect Dis* **1985**; 7:244–56.
46. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. *Lancet* **2015**; 385:1136–45.
47. van den Bergh ETAM, Hussein GM, Keuter M, Dolmans MV. Outcome in three groups of patients with typhoid fever in Indonesia between 1948 and 1990. *Trop Med Int Health* **1999**; 4:211–5.
48. Crump JA. Typhoid fever and the challenge of nonmalaria febrile illness in sub-Saharan Africa. *Clin Infect Dis* **2012**; 54:1107–9.
49. Devleeschauwer B, Haagsma JA, Angulo FJ, et al. Methodological framework for World Health Organization estimates of the global burden of foodborne disease. *PLoS One* **2015**; 10:e0142498.
50. Crump JA, Ram PK, Gupta SK, Miller MA, Mintz ED. Analysis of data gaps pertaining to *Salmonella enterica* serotype Typhi infections in low and medium human development index countries, 1984–2005. *Epidemiol Infect* **2008**; 136:436–48.
51. Britto C, Pollard AJ, Voysey M, Blohmke CJ. An appraisal of the clinical features of pediatric enteric fever: systematic review and meta-analysis of the age-stratified disease occurrence. *Clin Infect Dis* **2017**; 64:1604–11.
52. Hald T, Aspinall W, Devleeschauwer B, et al. World Health Organization estimates of the relative contributions of food to the burden of disease due to selected foodborne hazards: a structured expert elicitation. *PLoS One* **2016**; 11:e0145839.
53. Metcalf CJ, Farrar J, Cutts FT, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. *Lancet* **2016**; 388:728–30.