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Typhoid fever

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Abstract

Typhoid fever is an invasive bacterial disease associated with bloodstream infection that causes a high burden of disease in Africa and Asia.Typhoid primarily affects individuals ranging from infancy through to young adulthood. The causative organism, *Salmonella enterica* serovar Typhi is transmitted via the faecal-oral route, crossing the intestinal epithelium and disseminating to systemic and intracellular sites, causing an undifferentiated febrile illness. Blood culture remains the practical reference standard for diagnosis of typhoid fever, where culture testing is available, but novel diagnostic modalities are an important priority under investigation. Since 2017, remarkable progress has been made in defining the global burden of both typhoid fever and antimicrobial resistance; in understanding disease pathogenesis and immunological protection through the use of controlled human infection; and in advancing effective vaccination programmes through strategic multi-partner collaboration and targeted clinical trials in multiple high-incidence priority settings. This primer article thus offers a timely update of progress and perspective on future priorities for the global scientific community.

[H1] Introduction

Typhoid fever, also known as typhoid, is a serious invasive infection involving the blood-stream and deep reticulo-endothelial tissues. The organism responsible for the clinical syndrome of typhoid fever, *Salmonella enterica* subsp. *enterica* serovar Typhi (*S.* Typhi), is found within the Enterobacterales family. *S.* Typhi is a rod-shaped, Gram-negative, facultative anaerobic bacteria within the *Salmonella* genus, and is host-restricted to humans[1].

The WHO defines a confirmed case of typhoid fever as an individual with laboratory confirmation of *S.* Typhi by culture, or molecular methods such as detection of *S.* Typhi DNA, from a normally sterile site[2]. A suspected case of typhoid fever is defined as an individual with fever for at least three out of seven consecutive days in an endemic area, or following travel from an endemic area, or after a household contact with a confirmed case[2]. In endemic areas where appropriate diagnostics are lacking, clinical symptoms are relied upon for establishing a diagnosis. However, with numerous other infectious conditions presenting with a similar undifferentiated fever, clinical symptoms lack both sensitivity and specificity[3].

Typhoid fever was the first human disease in which asymptomatic carriage was demonstrated, in 1904, to be a source of disease transmission,[4] including in the famous case of Mary Mallon[5]. Generally, ~2–5% of acute typhoid illnesses are thought to develop asymptomatic chronic carriage[6]. Chronic carriage is defined as apparently healthy individuals with evidence of *S.* Typhi shedding in stool at least 12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms, following a laboratory confirmed episode of acute disease, or alternatively, two positive stool samples for *S.* Typhi 12 months apart.[2]

S. Typhi is transmitted via the faecal-oral route crossing the intestinal epithelium and disseminating to systemic sites. Blood culture, where available, remains the practical reference standard for diagnosis of typhoid fever[7]. Timely administration of appropriate antimicrobials is the mainstay of treatment for typhoid fever; however, with escalating antimicrobial resistance, treatment has become challenging in some parts of the world[8]. With improvements in sanitation infrastructure, drinking water quality, and enhanced food safety procedures the incidence of typhoid fever can be reduced.[9,10] However, in some low-resource settings, the comprehensive changes required in setting up such infrastructure

may take decades or even generations, and hence, the burden of disease from infancy through to young adulthood, remains unacceptably high.

The term 'enteric fever' encompasses both typhoid fever and the clinically similar syndrome caused by *Salmonella enterica* serovars Paratyphi A, B, or C (*S.* Paratyphi A, B, C). A full description of paratyphoid fever is beyond the scope of this primer, but it is mentioned in brief where there are relevancies, similarities, or contrasts — in particular for *S*. Paratyphi A, which accounts for ~25% of enteric fever cases in South Asia[11]. *Salmonella* serovars other than *S.* Typhi and *S.* Paratyphi A, B, or C are known as non-typhoidal *Salmonella* (NTS). Although NTS can cause a severe invasive syndrome (iNTS disease), which is particularly prevalent among African children, a description of NTS disease is also beyond the scope of this Primer.

In this Primer, we discuss the epidemiology of typhoid fever, detailing the burden and pattern of disease, modes of transmission, and risk factors for infection. Furthermore, we explore the literature on *S.* Typhi bacterial genomics as well as pathogenesis and the host response to infection. Finally, we outline the current patterns of antimicrobial resistance globally and the antimicrobial treatment options available. As typhoid has a variable and often non-specific clinical presentation, we emphasize the need for improved diagnostics for clinical use and epidemiological use.

[H1] Epidemiology

[H2] Reservoir, source, and mode of transmission

S. Typhi is a human-restricted pathogen with no non-human animal reservoir[12]. *S.* Typhi is shed in human faeces from sites of infection in the gallbladder and small bowel. In high-incidence areas with poor sanitation infrastructure, the major source of new infections is indirect transmission via water and via food contaminated with the faeces[13] of an infected person, who might shed the bacteria during acute infection, convalescence, or chronic carriage. As typhoid fever incidence declines within a specific population, the treatment of chronic carriers with antimicrobials and in some cases, cholecystectomy, might become necessary to prevent new infections. Studies have reported direct transmission of *S.* Typhi associated with oral-anal sex[14]. In addition, *S.* Typhi may also survive outside the human host for extended periods without evidence of multiplication[15] in a viable, non-culturable state, contributing to persistence and transmission over large distances and extended time

scales[16]. Changes in expression of *S.* Typhi genes involved in metabolism and the respiratory chain may provide insights into the mechanisms for survival of *S.* Typhi in aqueous and other environments[17]. Improvements in the sensitivity of detection of *S.* Typhi in environmental samples by nucleic acid amplification have enhanced our understanding of the role of environmental contamination in community-level risk of typhoid fever[18].

[H2] Measuring disease burden

Studies have established *S.* Typhi as the leading cause of community-onset bloodstream infection in south and southeast Asia[19] and an important albeit less prominent cause in Africa[20,21]. Since 2020s, the number and geographic representativeness of studies of enteric fever and typhoid fever incidence and outcome has improved greatly[22-26], as have approaches to extrapolating incidence,[27-30] and modelling burden of disease[31].

In 2017, typhoid fever was estimated to cause 10.9 (95% uncertainty interval, UI 9.3–12.6) million illnesses globally and 116,800 (95% UI 65,400–187,700) deaths globally[31]. The global case fatality ratio is estimated at 0.95%.

Based on population-based cohorts and national surveillance data in medium-incidence and high-incidence regions combined with registration sources in low incidence regions, global incidence of enteric fever was estimated to be 197.8 (95% UI 172.0–226.2) per 100 000 person-years[11]. Typhoid-specific global incidence is estimated to be 130.96 (95% UI 83.94-199.55) per 100 000 person years (**Figure 1**).[32]

Considering variation by super-regions, defined as areas of the world grouped by epidemiological similarlity and geographical proximity, south Asia had the highest age-standardised incidence rate of enteric fever (549, 95% UI 481–625, cases per 100 000 person-years) and the largest number of illnesses (10.3 million, 95% UI 9.0–11.7), accounting for 71·8% of global illnesses in 2017[11]. Southeast Asia, east Asia, and Oceania combined accounted for 14·1% of enteric fever illnesses (2.02 million, 95% UI 1.82–2.23) with an incidence ranging from 51.0 (east Asia) to 219.8 (southeast Asia) per 100,000 person-years. Sub-Saharan Africa accounted for 12·1% of enteric fever illnesses (1.73 million, 95% UI 1.45–2.06), and had an incidence ranging from 151–161 per 100,000 person-years in West and East Africa respectively, to 2.3 per 100,000 person-years in southern Africa[11].

To estimate burden of disease, a natural history approach is undertaken, which includes collation of studies of typhoid incidence using active population-based surveillance, or

hybrid surveillance methods, and extrapolating to areas without data[33,34,35]. In addition, the prevalence of major complications such as intestinal perforation, and the case fatality ratio[36,37] are applied to estimate disability and death owing to typhoid fever[31]. Overall, in 2017, enteric fever was responsible for 8.4 (95% UI 4.7 – 13.6) million disability-adjusted life years, comprising 8.3 (95% UI 4.6 - 13.4) million years of life lost and 105,000 years lived with disability)[11].

[H2] Risk factors

[H3] Age

In high-incidence and medium-incidence endemic settings, typhoid fever is observed from infancy onwards. Globally the disease peaks at 5–9 years of age, however, this average conceals considerable heterogeneity in incidence by age between regions and countries[11]. The peaks and decline in the incidence of typhoid fever with age in endemic settings are believed to be related to the rate at which susceptible individuals acquire infection and, therefore, the acquisition of immunity cumulatively from natural infection and repeated subclinical or asymptomatic exposure to the pathogen[38]. This means that across these age-bands there is considerable variation in age-distribution by location. For example, incidence may be high or even reach peak levels among infants in very high incidence areas, but peak incidence might be observed in older children or even young adults, in areas of medium incidence. Incidence subsequently declines gradually with age through adulthood and incidence is typically low in all elderly populations[31]. Re-infection, as opposed to relapse, has been documented, suggesting only moderate levels of protection conferred by an episode of clinical infection[39].

[H3] Environmental exposures.

A systematic review and meta-analysis of case-control studies evaluated associations between typhoid fever and water, sanitation and hygiene (WASH) and food exposures.[40] The authors identified 19 manuscripts describing 22 case-control studies, with 20 studies (90.9%) having medium or high risk of bias. In the meta-analysis, good hygiene and water treatment were most strongly associated with protection from typhoid fever (OR = 0.52 and 0.59, respectively), whereas poor hygiene and untreated water were most strongly associated with the risk of typhoid fever (OR = 2.2 and 2.4, respectively). Of the sanitation factors household latrine availability and use, safe waste management, unsafe waste management, and open defecation, unsafe waste management was significantly associated

with typhoid fever (OR = 1.6, 95% CI = 1.3–2.0). Hygenic food practices were significantly associated with decreased odds of typhoid fever (OR = 0.74), and risky food practices and consuming food or drink outside the home were associated with significantly higher odds of typhoid fever (OR = 1.6–1.7) than consuming home-based meals. Dairy, ice cream and fruits, and juices were significantly associated with typhoid fever (OR = 1.4–1.5)[40]. In a cluster randomized controlled trial of typhoid conjugate vaccine (TCV), living in a household with better WASH practices at baseline was associated with a significant reduction in the incidence of typhoid fever independent of vaccine intervention[41]. By contrast, in typhoid non-endemic countries, cases of typhoid fever were almost exclusively related to recent travel, contact with a traveller from an endemic country, or exposure to food prepared by a chronic carrier[42].

[H3] Human genetic factors.

A genome-wide association study performed among individuals with and without blood culture-confirmed enteric fever in Vietnam showed a strong association of rs7765379, a marker mapping to the HLA class II region, in proximity to HLA-DQB1 and HLA-DRB1, with an increased risk of infection[43]. This finding was replicated in a large cohort in Nepal and in a second independent study from Vietnam.[43] HLA-DRB1 was implicated as a major contributor to resistance against enteric fever, likely mediated by antigen presentation.

[H3] Seasonal and environmental factors.

Improvements in WASH and food exposures and increased use of TCV in typhoid-endemic countries, are likely to strengthen typhoid fever prevention and control. An analysis of seasonal patterns of typhoid and paratyphoid fevers observed a distinct seasonal pattern by latitude, with seasonal variability in incidence, more pronounced further from the equator[44]. The investigators found evidence of a positive association between preceding rainfall and enteric fever among regions 35°–11°N and a positive association between higher temperature and enteric fever incidence across most regions of the world. The underlying mechanisms that drive the seasonality of typhoid fever are poorly understood. The impact of climate change that contribute to faecal contamination of water and food, such as flooding or water shortages that increase dependence on unsafe water and deterioration in food safety might likely be associated with an increased risk of typhoid fever[45-47].

[H2] Pathogenic variants

Since the 1900s, phage typing has identified distinct variants of *S.* Typhi and *S.* Paratyphi [48,49]. Global diversity studies have shown that both pathogens harbour multiple distinct phylogenetic lineages, which are linked to specific geographic regions[50,51]. However, no evidence exists showing association of different *S.* Typhi or *S.* Paratyphi A variants with demographic factors such as age or sex[52,53]. Futhermore, the variants also do not exhibit differences in disease presentation or severity. Currently, pathogen genome sequencing have replaced phage typing and *S.* Typhi variants have been defined and identified using the GenoTyphi genotyping scheme, which was first developed in 2016 using ~2,000 pathogen genome sequences from 65 countries[54]. This scheme is regularly updated to reflect newly-identified variants or genotypes; for instance, the latest updates to the scheme (December 2022) were based on analyses of 13,000 genomes from 111 countries by the Global Typhoid Genomics Consortium[55,56]. These data provide a comprehensive view of the distribution of *S.* Typhi variants across different parts of the world, although some regions, especially Central and Northern Africa, Western Asia and Latin America, still lack sequence data. The distribution of variants is quite distinct by region (**Figure 2**)[57]. For example, genotype 4.3.1 (previously known as H58) dominates the pathogen population in South Asia (where it is thought to have emerged in the early 1990s)[58] and Eastern Africa (where it is thought to have been introduced multiple times in the last 10–20 years)[52], but is rare elsewhere. In Western Africa, the dominant genotypes are 3.1.1 and 2.3.1(ref[59]), whereas the dominant variants are 2,2.5 and 3.5 in Central America and South America[60,61]. In addition, island nations have their distinct genotypes — 3.5 in Samoa, 3.5 and 4.2 in Fiji, 4.2 and 2.1.7 in Papua New Guinea)[55,62,63]. The reason for geographic separation of variants is not fully understood, although human migration patterns might be the driving factor as *S.* Typhi is a human-restricted pathogen[64]. For example, the transfer of 4.3.1 to Eastern Africa could be linked to frequent migration of South Asians to Kenya and neighbouring countries in East Africa, whereas the distinct *S.* Typhi populations in Western Africa could reflect greater stability of communities within that setting.

[H1] Mechanisms/Pathophysiology

Non-typhoidal *Salmonella enterica (S. enterica)* serovars cause foodborne gut luminal inflammation and enterocolitis in healthy humans. However, *S.* Typhi once ingested can

rapidly cross the intestinal epithelium and disseminate to systemic sites, including the liver, spleen, bone marrow, and gallbladder[1] **(Figure 3)**. *S*. Typhi is unusual among *S. enterica* serovars in that it harbours an exopolysaccharide capsule known as Vi — the target of modern conjugate vaccines[65]. The Vi capsule is hypothesized to be crucial in *S.* Typhi pathogenesis; however, *S.* Paratyphi A causes a clinically indistinguishable infection despite lacking a Vi capsule, and these two human-restrictive invasive serovars do not share any additional or unique virulence factors[66]. Unlike non-typhoidal serovars that have a broad host-range among vertebrates, the genomes of serovars Typhi and Paratyphi A show evidence of functional gene loss, characteristic of host-restricted adaptation. Approximately 4% of *S.* Typhi and *S.* Paratyphi A genes carry these inactivating mutations, known as pseudogenes, compared with ≤1% in other non-typhoidal *S. enterica* serovars[67-70].

[H2] Insights from disease models

[H3] Infection of intestinal epithelium and dissemination to tissues.

Owing to the human-restricted nature of *S.* Typhi and *S.* Paratyphi A, much of the foundational understanding of typhoid pathogenesis has come from the study of mice infected with the 'generalist' serovar *S. enterica* serovar Typhimurium (*S.* Typhimurium) causing an invasive illness. This has elucidated a range of pathogenic mechanisms, and been considered a helpful model of typhoid. Furthermore, a range of related *in vivo* and *ex vivo* models have yielded important mechanistic insights into the complex interplay between the pathogen, the microbiota and the host response[70] . Following oral ingestion by mice, generalist non-typhoidal serovars survive gastric acidity and evade colonisation resistance by inducing inflammatory competition with the resident microflora, thereby altering the metabolic landscape in the lumen to optimise access to luminal host-derived resources such as oxygen, nitrate, tetrathionate and lactate[71]. *S.* Typhi , by contrast, is a stealth pathogen that employs several adaptation techniques to rapidly cross the gut epithelium, inducing minimal inflammation[66,72]. *S.* Typhi possesses the regulatory locus, *TviA*, encoding a protein with a complex counter-balanced regulatory function, which downregulates flagellin-associated inflammation and upregulates expression of the Vi capsule polysaccharide that mediates immune evasion[73]. The genes encoding the Vi capsule comprise the *viaB* locus within the *salmonella* pathogenicity island 7 (SPI-7), which also encodes the type III secretion system (T3SS) effector, SopE and a type IVB pilus[74].

Invasive salmonella serovars, in a susceptible host, can potentially cross the intestinal barrier by a multiplicity of routes, which include direct invasion of enterocytes, invasion by a transcellular route, direct uptake by dendritic cells across the epithelium or invasion of specialised antigen-sampling epithelial microfold cells (M cells). The M-cells overlie the organised lymphoid tissue of Peyer's patches, found particularly in the terminal ileum[75]. Salmonellae are transported via M cells to be presented to B cells and dendritic cells that reside within the microfolds in Peyer's patches[76]. Chronic infection of the lymphoid tissue in human intestinal Peyer's patches is a key element of pathogenesis, which acts as a source of ongoing enteric shedding in the stool and transmission. Chronic infection may also lead to necrosis of the Peyer's patch tissue and consequently, intestinal perforation — a serious complication of typhoid fever.

Once salmonellae have gained access to the host circulation causing a transient asymptomatic primary blood stream infection, they can disseminate to different organs by several mechanisms[77]. During extracellular vascular dissemination in the circulation, the Vi capsule inhibits phagocytosis and confers serum resistance, likely by shielding the surface lipopolysaccharide O-antigen from antibodies[78]. In addition, the ability to survive and disseminate intracellularly is a key pathogenic strategy and bacteria are also translocated from the gut within $CD18^{+}$ cells. This cellular population encompasses the reticulo-endothelial system including monocyte or macrophages, dendritic cells and polymorphonuclear leukocytes, and phagocytes in the liver, spleen and bone marrow[67]. Within minutes of contact with phagocytic cells, invasive salmonella are internalized into the salmonella-containing vacuole[67], a highly specialised modified phagosome that prevents endosomal fusion with the phagocyte oxidase complex, thus establishing a chronic, deep-seated intracellular reticuloendothelial infection[66]. This established infection results in a persistent secondary blood stream infection associated with high fever. Salmonellae to thence enter and colonise the gall bladder, particularly if there are gallstones or other structural abnormalities, providing an important niche from where they may be shed back into the gastrointestinal tract in bile. This is the hallmark mechanism of chronic carriage of typhoid in human disease, enabling ongoing community transmission of the pathogen to new hosts. This re-infection of the upper gastrointestinal tract may also result in re-infection of Peyers patches, leading to necrosis of tissue and consequently, intestinal perforation — a

serious complication of typhoid fever requiring surgery, which may be accompanied by a tertiary blood stream infection with a range of enteric micro-organisms.

[H2] Controlled human infection model

A controlled human infection model (CHIM) for study of typhoid infection, was established at Oxford University in 2011 to further our understanding of disease pathogenesis and accelerate the development of candidate vaccines[79]. The CHIM model involved deliberate infection of healthy adult volunteers with an antibiotic-sensitive strain of *S.* Typhi, manufactured under Good Manufacturing Practice , originally derived from the gallbladder of a woman with chronic typhoid infection in Maryland in the 1950s[79,80]. After screening and informed consent procedures, participants ingested 10,000 colony-forming units (CFU) of *S.* Typhi in a bicarbonate solution. Approximately two thirds of individuals developed a fever for ≥12 hours and/or bacteraemia over the next 2 weeks (median time to onset was 8 days), thus meeting the study definition of typhoid fever and triggering cessation of infection with oral antibiotics[79]. A similar model was established to study paratyphoid infection, although 1,000 CFU of *S*. Paratyphi A were sufficient to cause consistent infection (60%)[81]. In the paratyphoid infection model, the proportion of individuals with bacteraemia and the cytokine responses of participants were similar to those in the typhoid infection model. However, bacteraemia was more prolonged (median 53 hours) and blood-culture positive asymptomatic infection was more common (55%) in individuals with paratyphoid fever than in individuals with typhoid[81].

[H3] Inflammatory response.

After ingestion of the bacteria, the typhoid model showed evidence of transient but asymptomatic bacteraemia in the first 24 hours documented by detection of DNA in peripheral blood[82], This bacteraemia might represent the initial transit of bacteria from the gut mucosa to the lymphoid tissues prior to the incubation period. The initial DNAaemia is associated with a systemic cytokine response, notably consisting of sCD40L, fractalkine (CX3CL1), GROα, IL1RA, EGF and VEGF, regardless of whether the individual later goes on to develop overt typhoid disease. This cytokine response may represent inflammatory perturbation at the gut mucosa, perhaps implying that the infection is limited to the mucosa, but could also be consistent with invasive infection even among those who do not go on to show evidence of overt infection[83]. Onset of clinical invasive disease was heralded by a gradual fall in eosinophil count over the 5 days preceding onset of symptoms, followed

by a fall in total white cell count, lymphocytes, neutrophils and platelets after the onset of clinical disease[79]. Whether these changes represent successful deployment of an appropriate immune and inflammatory response to the infection or a failure of an appropriate protective response are not clear. Almost all individuals had positive blood cultures associated with diagnosis of infection in the model, with a median of 1 CFU per ml of blood detected.[79]

After the onset of febrile symptoms, the profile of transcriptomic responses reflected the presence of strong type I and II interferon signals that were associated with bacteraemia in the study[83]. Evidence shows that this interferon signalling interfered with tryptophan metabolism, which might indicate that part of the host response exists to limit bacterial growth. As a component of the acute innate immune response to infection, studies have shown an increase in hepcidin levels increased and decrease in blood iron levels.Limiting the iron availability for extracellular bacteria in the blood and concomitantly increasing iron availability in macrophages supporting survival of internalised bacteria is a characteristic feature of *S.*Typhi infection[84] .

[H3] Antibody response.

Among those challenged with *S.* Typhi who progressed to develop clinical disease, IgG, IgM and IgA responses against H (flagellar) antigen and lipopolysaccharide were detected in the peripheral blood, but no measurable anti-Vi antibody response were detected in these previously unexposed individuals[79]. Responses in the CHIM were further probed using a 250-antigen array, and serodiagnostic signatures containing flagellin, OmpA, HlyE, sipC, and IgG, IgM and IgA antibody responses against lipopolysaccharide could distinguish typhoid from other febrile illnesses in an endemic setting[85] . IgA against lipopolysaccharide antigen performed particularly well as a diagnostic marker in the model. In addition, a set of five gene expression profiles that could distinguish individuals with typhoid infection from other febrile illnesses were identified using the CHIM[86].

[H3] Role of typhoid toxin.

Studies have shows that typhoid toxin induced some of the hall mark clinical features of the disease in murine models, suggesting that the toxin may be an important virulence factor for *S.* Typhi[87,88]. However, the toxin also found in other typhoidal and non-typhoidal salmonellae including serovars that do not cause the clinical syndrome of enteric fever[68,89,90]. To assess the virulency of the toxin, volunteers were challenged either with a

toxin-negative or wild-type strain and no difference was found in the proportion of individuals developing typhoid between the two groups. Unexpectedly, bacteraemia was more prolonged in the toxin-negative group than in the wild-type group. These observations indicate no role for typhoid toxin in imparting susceptibility to typhoid infection[91].

[H3] Infection-derived immunity.

Immunity acquired from *S.* Typhi infection is likely an important factor to be considered when understanding the impact of vaccination on transmission of the pathogen. Whilst modelling studies include acquisition of natural immunity as an important variable, few data are available on the level and duration of protection afforded by clinical disease episodes[92,93]. After prior CHIM infection (median 19 months previously, range 12–67 months), volunteers who underwent rechallenge with the same serovar as their initial challenge (homologous challenge with *S.* Typhi or *S.* Paratyphi A) had a moderately reduced risk of developing typhoid (36%) or paratyphoid (57%), but no protection was conferred by challenge of the alternative organism(heterologous cross-challenge)[38]. In those who did develop enteric fever, no difference in symptoms was found between naïve individuals (those not previously challenged) and those who had previously been challenged. Interestingly, baseline anti-lipopolysaccharide, anti-H and anti-Vi antibody levels were similar between the naïve and rechallenged groups, and no obvious boost in antibody was observed in those with prior exposure[38].

[H3] Stool shedding.

Six typhoid and paratyphoid CHIM studies with 4,934 stool samples were analyzed to identify factors that might reduce stool shedding and potentially reduce transmission in field settings[94]. Prior infection in those who were rechallenged in the CHIM was associated with reduced shedding (OR 0.30; 95% CI: 0.1–0.8) as was prior vaccination with a Vi-containing vaccine (OR 0.34, 95% CI: 0.15–0.77 for Vi polysaccharide vaccine; and OR 0.41, 95% CI: 0.19–0.91 for TCV)[94]. A non-significant reduction in stool shedding was associated with the live oral Ty21a vaccine[94]. The Oxford CHIM has been used in assessing vaccine efficacy of a number of typhoid vaccines (Box 1).

[H2] Antimicrobial resistance

Antimicrobial resistance is common in both *S.* Typhi and *S.* Paratyphi A, and is typically driven by local overprescription of antibiotics[95,96]. Multidrug resistant (MDR) *S.* Typhi is defined as resistance to the combination of three first-line treatments — chloramphenicol,

ampicillin and trimethoprim-sulfamethoxazole. MDR *S.* Typhi, a clinical problem since the 1980s, emerges through the simultaneous acquisition of multiple resistance genes encoded on a single transmissible plasmid, which can be transferred between bacterial species and strains[97]. By the 1990s, in parts of south and southeast Asia the majority of *S.* Typhi infections were MDR[98], prompting a switch to fluoroquinolones and azithromycin as the mainstays of treatment. However, fluoroquinolone resistance is now highly prevalent in these regions, mostly owing to *gyrA* and *parC* mutations in [58,99]. Extensively-drug resistant (XDR) *S.* Typhi, defined as the combination of MDR plus resistance to fluoroquinolones and third-generation cephalosporins, has now emerged. A large outbreak of XDR *S.* Typhi was reported in Pakistan in 2016 and the corresponding variant (4.3.1.1.P1), which has spread throughout the country, caused the majority of typhoid cases reported there in 2018–2019 (Ref[100,101]). Although this XDR variant has been detected in other countries, its incidence is usually linked to travel to Pakistan[102,103]. The prevalence of MDR *S.* Typhi has declined <10% in India and Nepal. However, as MDR plasmids still circulate amongst other salmonellae in these regions, return to previous drugs is not favoured as it might prompt a re-emergence of MDR and subsequently, XDR *S.* Typhi. Azithromycin resistance has been reported, mainly in south Asia, but remains rare (<1%)[57]. By contrast, in sub-Saharan Africa, MDR *S.* Typhi is common in most countries and fluoroquinolone resistance is increasing in countries where this drug class is overprescribed[104]; azithromycin and XDR strains are, however, extremely rare[52,59,95,96]. *S.* Paratyphi A infections are rarely MDR, but are almost always fluoroquinolone resistant[49,51,95]. Azithromycin resistance is reported in *S.* Paratyphi A in south Asia but, similar to *S*. Typhi, remains rare .

[H1] Diagnosis, screening, and prevention

[H2] Diagnosis

One major obstacle to controlling typhoid fever is the absence of reliable and easily deployable diagnostics. In most resource-constrained settings, diagnosis is based on clinical symptoms and in most cases, the Widal test, which is non-specific, is used[105]. Most patients with typhoid fever present with nonspecific clinical features, with fever predominating, alongside symptoms such as malaise and headache[106]. Hence, differentiating typhoid fever from other febrile illnesses, such as malaria, dengue or scrub typhus, can be challenging.[12] Multiple studies in typhoid-endemic areas in Asia have demonstrated that relying on clinical

features to diagnose typhoid fever is unreliable with low specificity (< 15%) and positive predictive values (≤ 10%)[107,108].

Efforts are in progress to create a benchmark specification for an improved diagnostic test for typhoid fever. Ideally, this test would fulfill several key criteria — it would be inexpensive (for instance, costing <1 dollar), highly accurate (with a high sensitivity and specificity), quick (results available in <15 minutes) and user-friendly, requiring no data-interpretation, minimal training or sample processing, and not dependent on a stable water or power supply. A test that meets these standards would markedly improve the clinical diagnosis and management of typhoid fever, thereby reducing its morbidity and mortality. Improved diagnostics will also contribute to combat antimicrobial resistance. The available tests for typhoid do not currently meet these specificationsand promising assays are in development.

[H3] Culture testing.

A positive culture test from a normally sterile site (blood or bone marrow) is considered the reference standard for typhoid fever. However, the results might take several days and culture testing requires substantial laboratory capacity, which is not widely available in resource-constrained areas. The sensitivity of culture depends on the specimen type, prior antimicrobial use, timing of collection and sample volume owing to differences in bacterial burden at systemic sites[7]. For example, the organism burden in bone marrow is orders of magnitude higher than in the peripheral blood (median of 10 vs. 0.5 colony forming units/mL, respectively)[109] and bacterial load in the blood peaks during the first week of infection[7]. Bone marrow culture has the highest sensitivity (>90%)[110] and bacterial load remains high in bone marrow for several weeks, but this method has limited clinical utility due to its invasiveness. Blood culture has a sensitivity of only 50–70%[7,111], and stool culture has a sensitivity of 30–40%[112]. In addition to having low sensitivity, a positive stool culture may indicate either acute disease, convalescent disease or chronic carriage and is, therefore, not considered diagnostic of current invasive disease.

[H3] Molecular testing.

Molecular diagnostics offer great promise to improve sensitivity and decrease time-to-result. Multiple nucleic acid detection methods have been developed including conventional, nested, multiplex, and real-time PCR and loop-mediated isothermal amplication; however, these methods share the same limitations as blood culture[113].

Moreover, current PCR-based methods require laboratory capacity, and the stochasticity of genomes in small blood samples can lead to false negatives[82,114]. Owing to the low magnitude of bacteremia in typhoid fever, a pre-culture may be required to improve sensitivity.

[H3] Novel serodiagnostics.

Commercially available serum-based diagnostics, including the Widal agglutination test and latest generation rapid diagnostic tests are widely available and detect antibodies against *S.* Typhi in serum or plasma. Although simple and fast, these tests have moderate sensitivity and specificity due to pre-existing antibodies from prior exposure and cross-reactivity[105]. In a Cochrane review of 37 typhoid rapid diagnostic tests, the best-performing assay, Tubex, had a sensitivity of 78% and specificity of 87%[105] and a prospective and hybrid retrospective study of 9 commercially available rapid diagnostic tests showed the best-performing test was Enterocheck with 73.8% sensitivity and 94.5% specificity[115]. These results underscore the need for improved tests that accurately detect the *S.* Typhi.

Advances in antigen discovery have revealed several novel antigen targets to improve serodiagnostic assays[85,116,117]. Many of these antigens were further validated in populations from Bangladesh and Nepal[118] and a promising rapid diagnostic test, namely, the DPP® Typhoid Assay has been developed. This assay is based on detecting *S*. Typhi lipopolysaccharide and HlyE-specific IgA and early studies demonstrate sensitivity and specificity of >90%[118]. Other novel typhoid diagnostic approaches currently being explored include host gene signatures or metabolite signatures, which can discriminate typhoid from other febrile illnesses[86,119].

[H2] Surveillance

Wastewater and sero-surveillance are powerful and low-cost tools that have been used to monitor community pathogen burden for several infections and are currently being evaluated for measuring *S.* Typhi exposure and transmission within populations. In addition, these approaches provide estimates of disease burden, which are not biased by care-seeking behaviours and measure both symptomatic and asymptomatic infections. Studies have demonstrated antibody levels to HlyE as an accurate serologic marker of acute typhoid infection[118,120]. A multisite study used population-based serologic data to HlyE antigen coupled with a new statistical modelling approach to estimate enteric fever incidence[120]. These estimates correlated well with blood culture-based etimates of incidence but were

generally >100-fold higher than the unadjusted blood-culture confirmed incidence, implying the rates of pathogen exposure and infection are far higher than recorded through clinical surveillance. An existing challenge in serosurveillance studies of typhoid fever is that the antigens presently used cannot differentiate *S.* Typhi from *S.* Paratyphi A. Anti-Vi IgG can discriminate these *Salmonella* serovars, however its effectiveness is limited by low seroconversion rates following S. Typhi infection and the prevalence of Vi antibody within endemic communities. The introduction of Vi-based TCV will further complicate its use in seroepidemiology, as Vi antibodies cannot distinguish active infection, immunity from natural infection or vaccine-induced immunity.[120,121] Environmental surveillance, which uses culture or PCR-based methods to detect *S.* Typhi shed by infected individuals in sewage or in water sources, does not have this limitation. However, the outcomes from environmental surveillance for *S.* Typhi has been mixed[18]. The organism burden of *S.* Typhi is much lower than for viral infections (for example, SARS CoV-2), which is reflected by the infrequent detection of *S.* Typhi in wastewater samples[18]. Ongoing studies are being conducted to ascertain if there is a correlation between environmental detection of *S.* Typhi and clinical incidence. If this correlation is positive, two cost-effective and scalable methods that could complement blood culture-based clinical surveillance will become available and expand typhoid surveillance to areas without access to blood culture. A potential limitation to consider, however, is that representative samples might be difficult to obtain from at-risk communities that lack sewage systems.

[H2] Clinical manifestations

Typhoid fever is an outpatient disease in most areas of endemicity and generally presents as undifferentiated febrile illness[3]. Symptoms of typhoid fever manifest 10–14 days following exposure and include generalized fever and malaise, abdominal pain with or without other signs such as headache, myalgias, nausea, anorexia, constipation and less commonly, diarrhoea **(Figure 4)**[106,122]. The fever is classically described as step-wise (that is, gradually increasing), manifesting in the first week of illness[123]. On clinical examination, hepatosplenomegaly is observed in 29–50% of cases; diffuse abdominal tenderness and a coated tongue (that is, a superficial white coating on the surface) is more common than other symptoms and is observed in 56–85% of cases[122]. Additionally, rose-spots (a blanching erythematous rash containing culturable *S.* Typhi) are reported in the historical literature[110]. The antibiotic era has changed some of the clinical features historically seen in typhoid

fever; as patients receive appropriate antimicrobial therapy, the prevalence of hepatosplenomegaly and rose spots has reduced[3,124].

[H3] Gastrointestinal complications

Severe complications, such as shock, jaundice, intestinal perforation, intestinal haemorrhage and encephalopathy, can occur if antimicrobial treatment is delayed or inadequate[36]. Intestinal perforation is commonly reported as a sequalae of severe typhoid infection, with the primary site of perforation occurring in the terminal ileum, resulting from necrosis of infected Peyer's patches[125,126]. Studies have documented increasing prevalence of intestinal perforation in outbreak scenarios and in regions with increasing antimicrobial resistance[127]. In this regard, the WHO have included guidance on the surveillance of intestinal perforation, recommending all instances to be recorded in typhoid endemic regions[2]. A systematic review of intestinal perforation in Africa found the case fatality rate to be between 4.6% to 75% in included studies; however, the majority of studies (79%) reported a fatality rate between 10% and 30%[126] . Intestinal perforation is treated by surgery, and another review estimated the mean duration of hospitalisation secondary to intestinal perforation to be 18.4 days[128].

[H3] Neurological manifestations.

Although rare, studies have reported numerous neurological manifestations of enteric fever, including typhoid meningitis and encephalopathy[129]. In 2009, a large outbreak of blood-culture confirmed typhoid fever with an unusually high burden of neurological complications (13%) and high mortality rate (4%) was reported from the Malawi-Mozambique border[130]. Dysarthria, ataxia, upper motor neuron signs and altered mental status were identified in >40 individuals.[130] Although, culturing *S.* Typhi directly from the cerebrospinal fluid is rarely performed, cortical irritation leading to clinical symptoms is hypothesized to be mediated by the typhoid toxin[131,132] .

[H3] Other complications.

Systematic reviews have highlighted other complications that occur in different age-groups of patients with typhoid fever. Hepatitis (36%), anaemia (71%) and leukocytosis (41%) are common in children <5 years of age, whereas altered mental status (30%), signs of upper respiratory tract infection (22%) and abdominal pain or tenderness (70%) are frequent in school-aged children[106,132]. Young children, <5 years of age, are more likely to present with diarrhoea than older children and adults, whereas constipation and intestinal perforations

are often observed in older age groups (>15 years) than children[106,132]. In addition, respiratory symptoms (cough or bronchopneumonia) or neurologic complications (such as, encephalopathy and febrile seizures) are more commonly seen in children than adults. These reviews also reported geographical heterogeneity for common complications associated with typhoid fever, with anaemia being more prevalent in South Asia than other regions and abdominal distension, ileus and intestinal perforation more prevalent in sub-Saharan Africa than the rest of the world[36,106].

The estimated pooled prevalence of all complications (defined as any unfavourable evolution of the disease) in hospitalised patients was 27% (95% CI, 21– 32%)[133] with a mean overall case fatality of 4.45% (95% CI 2.85–6.88%)[134]. The manifestation and severity of typhoid fever can differ depending on the patient's age and geographical region. Children bear the highest disease burden, with higher case fatality rate and complications in Africa (mortality 5.4%) than in Asia (mortality 0.9%)[25,36]. In Africa, mortality from intestinal perforation was estimated to be 19.7% compared with only 4.6% in Asia[36]. This reason for differential mortality rates between Africa and Asia is likely to be multi-factorial. For example, delays in accessing healthcare, receiving an accurate diagnosis and administering appropriate treatment owing to poor healthcare infrastructure all probably contribute to such differences[36].

[H2] Chronic carriage

Approximately ~2–5% of acutely infected individuals are thought to develop typhoid chronic carriage. However, with the usage of antimicrobials, the evolution to chronic carriage might be less[135,136].

To establish long-term carriage, organisms must enter the biliary tract either directly by ascending through a malfunctioning sphincter of Oddi, or indirectly via the liver during systemic infection[137]. Epidemiological investigations through case-control studies, and ultrasound imaging in mice and humans, have shown the association between chronic carriage and the development of bacterial biofilm *S.* Typhi on gallstones within the gallbladder[138-140]. This association is further supported by data from different parts of the world showing that prevalence of chronic carriers increase with age and are predominantly female. These two characteristics are also primary risk factors for the development of gallbladder pathology[42,135,139].

Studies have shown the importance of carriage in low incidence, non-endemic settings through multiple outbreaks, which have been traced to a chronic carrier often responsible for food preparation[141]. However, the contribution of carriers to ongoing transmission within endemic sites and the diagnosis of these individuals remains unclear. Stool shedding of the pathogen is intermittent and at a low level, which makes detection through serial stool culture both programmatically difficult and unreliable[142].

Isolating the bacteria directly from the gallbladder is the gold standard for diagnosing carriage. This procedure might be possible in individuals undergoing cholecystectomy but is highly impractical at a public health level owing to the invasive nature of the procedure. The duodenal string test, which involves passing a capsule into the stomach and a nylon string to pass through the pylorus and duodenum, enabling the collection and subsequent culture of duodenal and bile fluid, has been used historically for both the diagnosis of acute and chronic typhoid[143,144]. However, yet again, this test is impractical at a public health level owing to its invasiveness and inconvenience[42].

Serological screening for chronic carriage using anti-Vi antibody has been successful in non-endemic sites[141,145], but in medium to high incidence area, where regular infection or exposure to the pathogen increases the Vi capsule titre, the screening results have been mixed[146-148]. Studies to identify novel serological markers of acute typhoid and carriage, along with transcriptomic and a metabolomic profile, which could improve the prospective diagnosisare underway[149-151].

[H2] Prevention

[H3] Improved water, sanitation and hygiene

Improvements in water and sanitation infrastructure, where human waste is removed safely from a population and uncontaminated drinking water is provided, has been shown to reduce typhoid incidence in many developed countries.[9,10] This approach often requires large centralised, government-led initiatives with high levels of financial investment. Typhoid incidence remains high in areas of the world that lack reliable clean water and sanitation but where such infrastructure projects are challenging to deliver and maintain. Evidence from Chile and Kenya has shown that in high typhoid incidence settings, improving drinking water quality alone may not be sufficient to reduce disease incidence.[152,153] In Chile, the irrigation of crops with untreated raw sewage was identified as a major factor of maintaining typhoid transmission and, once this practice was prohibited, in combination

with other interventions, such as typhoid vaccine campaigns, disease incidence was reduced.[152,154] As demonstrated in Chile, behaviouoral change can be a feasible and affordable option in reducing disease burden with improved water sources, improved basic hygiene and treated water highlighted as areas that reduce disease burden after systematic review.[155] New approaches using point of collection disinfection technology may provide a low-cost and easy to use alternative in parts of the world where water supply is intermittent and faecal contamination remains a risk.[156]

[H3] Vaccine development

Vaccines may be a useful adjunctive strategy to WASH improvement to prevent morbidity and mortality from typhoid fever. Although typhoid vaccines have been in use since the late 19th century, early vaccines were not fit-for-purpose for widespread deployment. For example, the systemic and local side effects from the earliest heat-killed whole cell vaccines rendered them unusable in young children.[157,158]. Subsequently, two more formulations were developed; a live attenuated Ty21a vaccine and a Vi-Polysachharide (Vi-PS) vaccine. A meta-analysis demonstrated a pooled efficacy of 50% for the oral live-attenuated Ty21a vaccine at the 3-year follow-up[159]. Typically, multiple doses of attenuated vaccine are required, and the capsule formation makes it difficult to administer the vaccine to children younger than 6 years of age. The Vi-PS is a parenteral vaccine containing the purified capsular Vi-polysaccharide antigen and studies demonstrated an efficacy of 59% for Vi-PS at 2 years[160]. Currently,Vi-PS is not licensed in children <2 years of age due to poor immunogenicity. Although these vaccines have been widely used for travellers, the limitations prevent their usage outside of outbreak control in low-income settings despite a WHO recommendation in 2008 for their use to improve typhoid control[158].

[H3] Typhoid conjugate vaccines

A new generation of typhoid conjugate vaccines (TCV) have become available, in which the Vi capsule is chemically conjugated to a protein carrier, thereby producing a T-cell-dependent response with a greater and longer-lasting immunogenicity than with non-conjugate vaccines, including younger children and infants from 6 months of age [161]. In 2018, the WHO published a recommendation for the use of TCV in countries with endemic typhoid, with priority given to countries with a high burden of disease, or high prevalence of antimicrobial resistance, or both[162]. Notably, TCV was the first vaccine to be recommended by the WHO based on its potential to prevent the spread of antimicrobial resistance. A

single dose of TCV is recommended for children from 6 months of age, introduced into routine immunization schedules alongside mass catch-up campaigns from the first or second year of life through to 15 years of age[162].

Licensure of the first TCV was based on an immunogenicity and safety trial from India,[163] with the first vaccine efficacy data coming from adults in a non-endemic setting, as part of the Oxford CHIM for typhoid.[164,165] Since then, data from several phase 2 and 3 clinical trials in diverse high-burden endemic settings confirm excellent safety, immunogenicity (including safe co-administration with other routine immunisations) and efficacy for single-dose TCV in children (Table 2).[166,167] Trials conducted in >100,000 children in Nepal, Malawi and Bangladesh yielded efficacy estimates of 79-85% in the first 1-2 years following receipt of TCV.[168, 169, 170,171] Longer-term efficacy data after >4 years of follow-up have shown an overall intention-to-treat efficacy of 78% from the Malawi cohort, suggesting durable protection.[172]

Notably, significant protection occurred in children <2 years of age, important for a vaccine that will be introduced into routine immunisation schedules in the first 2 years of life [170 171 173 174].

The trial in Bangladesh was cluster-randomized and did not demonstrate any significant additional indirect protection among non-vaccinated individuals. Vaccination campaigns across a wider age-range, to include adults, might be required in some epidemiological settings to achieve indirect effects.[175] Nevertheless, the individual protection afforded by TCVs between these three large vaccine efficacy trials, in comparable age-groups, and across three very epidemiologically diverse sites is strikingly consistent.

In addition, data have been published from post-vaccine introduction evaluations, from countries such as India,[176] Pakistan[177] and Zimbabwe.[178] Data from Pakistan provide confidence that TCV is highly effective against the XDR strain of *S.* Typhi, providing evidence that as well as reducing the burden of typhoid fever, it will have a positive impact on decreasing antimicrobial resistance.[179]

Although the safety, immunogenicity and efficacy of TCVs has been demonstrated in diverse populations, TCVs alone are unlikely to eliminate typhoid fever, as evidenced by the incidence rates in the vaccine groups of the trial populations. Thus, their use should be viewed as an important adjunct to improvements in WASH, as the latter has successfully eliminated typhoid fever in many countries around the world.[9,180,181]

[H1] Management

Antimicrobials have transformed typhoid from an illness that can have a mortality between 10 and 30% to an illness where symptoms resolve within a week with a case fatality ratio <1%[124]. The emergence of resistance to the commonly used antimicrobials for treating enteric fever have challenged this picture[182]. Antimicrobial resistance is associated with treatment failure, an increased risk of complications and an increased potential for transmission due to prolonged faecal shedding[124,183,184] . Treatment choices should take account of local antimicrobial resistance patterns, if known, and national guidelines where available[185].

[H2] Antimicrobial therapy

Most patients with enteric fever are treated with an oral antimicrobial as part of outpatient management in the first week of illness and typically recover within a week. The WHO Essential Medicines Expert Committee concluded on the core list of Essential Medicines List that a seven-to-ten-day course of either ciprofloxacin, ceftriaxone or azithromycin should be considered first-choice treatments for adults and children[186]. Ciprofloxacin is not a suitable choice in most parts of south Asia, and some areas of sub-Saharan Africa, because of widespread resistance [124,182]. Azithromycin is an effective alternative drug although sporadic reports of antimicrobial resistance have been reported[187,188]. In those admitted in hospital, parenteral ceftriaxone is a safe option, particularly when resistance to other drugs is uncertain. Oral chloramphenicol, amoxicillin and trimethoprim-sulphamethoxazole were commonly used prior to the 1990s, but multidrug resistance to these three antimicrobials emerged in the late 1980s and became widespread, preventing their usage[96].

Systematic reviews of the comparative efficacy of chloramphenicol, the fluoroquinolones (such as ciprofloxacin, ofloxacin and gatifloxacin), azithromycin and cephalosporins (such as ceftriaxone and cefixime) in typhoid fever treatment have been unable to draw firm conclusions on the presence or absence of important differences between the various antimicrobials[189-191]. Evidence from most of the randomised controlled trial is of low certainty owing to small trial size and methodological problems such as not double-blinded and conducted >20 years ago. The lack of diagnostic sensitivity of blood culture, the paucity of trials in the outpatient setting, the changing pattern of resistance over time and the lack of agreed core outcome indicators are further limitations.

[H2] Antimicrobial resistant strains

The outbreak of XDR *S.* Typhi in Pakistan in 2016 has impacted the usefulness of ceftriaxone in managing patients with typhoid[192]. These strains are resistant to chloramphenicol, ampicillin/amoxicillin, trimethoprim-sulphamethoxazole, ciprofloxacin and ceftriaxone/cefixime but susceptible to oral azithromycin and parenteral meropenem[100]. These infections are documented in other countries in travellers from Pakistan[102].Studies have also reported sporadic cases of ceftriaxone resistance distinct from those identified in Pakistan[193,194]. Clinicians treating patients with XDR *S.* Typhi have found no important differences in the clinical response between oral azithromycin alone, intravenous meropenem alone and a combination of azithromycin and meropenem[195]. Notably, the daily cost of meropenem in Pakistan was 15 times more than azithromycin.

[H2] Combination therapy

Studies have confirmed that *S.* Typhi can reside intracellularly and extracellularly, with high bacterial load in sites of the reticuloendothelial system, such as the bone marrow[109,196]. Antimicrobials used to treat typhoid fever should target all these locations. Combining azithromycin, which reaches very high intracellular concentrations but low extracellular concentrations[197], with a beta-lactam antimicrobial that is predominantly active in the extracellular compartment has been suggested as a better option for the treatment of typhoid fever. In an RCT of 105 adults with confirmed typhoid fever in Nepal, a combination of azithromycin and cefixime for outpatients and azithromycin and ceftriaxone for inpatients was superior to azithromycin alone, with shorter fever clearance times[198] A clinical trial examining the efficacy of a combination of azithromycin and cefixime in suspected cases of enteric fever in south Asia is ongoing[199].

[H2] Severe infections

In severe typhoid fever, supportive care such as, full intensive care provision, blood transfusion in the event of gastrointestinal haemorrhage and surgery in case of intestinal perforation and peritonitis, is critical to the outcome[200]. Following intestinal perforation, secondary blood stream infection may occur due to a range of pathogens from the gut lumen, requiring a repetition of blood culture and broadening of antimicrobial treatment. One RCT in Indonesia demonstrated that high-dose methyl-prednisolone reduced mortality in severe typhoid, characterised by altered consciousness and haemodynamic shock[201].

Methodological issues make it difficult to draw definitive conclusions from this study and further trialsare needed to address the effectiveness of prednisolone[202].

[H2] Chronic carriers

A systematic review of studies of the antimicrobial treatment of chronic carriage identifiedthat fluoroquinolones were effective in eradicating chronic carriage of susceptible isolates after a 28-day course[203] . The only double-blinded RCT performed showed an eradication rate of 92% in those given a 28-day course of norfloxacin compared with 11% in those given placebo. Six studies evaluated ampicillin or amoxicillin in a four-to-six-week course with eradication rates ~70%. Cholecystectomy may be an option where eradication has failed, particularly in the presence of structural biliary abnormalities including gallstones, which may provide a protected niche for bacteria; however, this decision should be weighed against the risk of surgical complications[124]. All these studies pre-date the emergence of widespread MDR and fluroquinolone resistance, and further clinical trials, for example, using azithromycin, are warranted to help guide modern management.

[H1] Quality of life

[H2] Cost of illness

Despite the potential acute effects and sequelae from typhoid fever, its impact on quality of life is not well documented. However, a number of studies have assessed the economic burden of typhoid in terms of costs to healthcare providers and to affected households in low-income and middle-income countries[204-208]. A review of economic evidence highlights the cost of hospitalisation as the most common expense reported in the literature. Costs per hospitalised case range from $159 to $636 in India, $233 in Nepal and $171 in Tanzania (2016 US$)[209-212]. Costs for treating outpatients ranged from $0 to $14.1 (2010 US$) [213]. Costs for treating outpatients ranged from $16 to $74 in India, and equalled $39 in Nepal (2016 US$).[204]

Studies have specifically studied the cost of intestinal perforations, a complication that may result from untreated typhoid or delayed access to care. For example,the additional surgical costs to repair an intestinal perforation, on average, were as high as $452 in Nigeria and $1,210 in India (2019 US$) [214,215]. These high costs are accompanied by longer hospital stays, 23 days on average in Nigeria and 19 days in India, which also increase a family's expenses[214,215].

The potential for higher cost of illness associated with MDR and XDR *S.* Typhi infection, requiring more expensive and less available treatments than for classical *S.* Typhi infection , is not well documented. Data from the XDR outbreak in Pakistan between 2016 and 2018 suggest that the cost of an episode of typhoid from XDR *S.* Typhi is 2 to 4 times higher than the cost of non-XDR *S.* Typhi infection[216].

Owing to the difficulty in diagnosing typhoid, seeking health care can be a long and costly endeavour for patients and their caregivers. Households often face indirect expenditures such as transportation, loss of household income, and food and subsistence costs related to seeking and receiving care, alongside direct out-of-pocket costs including diagnosis and treatments, such as medication. Typhoid predominantly impacts children <15 years of age, implying that a case of typhoid often results in parental absenteeism from work and a loss of income for caregivers, which can cause financial consequences for families. These expenses may reduce expenditures on other household spendings, which can affect investments in nutrition, education and other household needs, and trigger dissaving measures, resulting in long-term adverse socioeconomic impact.

Typhoid can represent a catastrophic cost to affected families, defined as expenses and loss of revenue due to seeking care or caring for sick children and family members that represents more than 40% of non-food monthly household expenditure. One study in Malawi reported that, despite free access to all government medical care and minimal out-of-pocket direct healthcare costs, 44% of households faced catastrophic illness costs mainly related to indirect costs and 16% of households experienced illness costs that were more than their total monthly income[217]. The median cost per case for inpatient care in patients with enteric fever was also determined as catastrophic for families in studies in Bangladesh, Nepal, and Pakistan[209-212]. Despite revealing the unfortunate societal costs involved in typhoid management, cost of illness estimates are essential for evaluation of vaccine cost effectiveness, to inform policy decisions **(Box 2)**.

[H1] Outlook

Since 2010, considerable progress has been made in the development and licensure of TCVs supported by robust evidence on safety and immunogenicity, innovative data on efficacy from the CHIM and field efficacy data from large clinical trials conducted in diverse populations at risk[218]. This compelling body of data has reaffirmed the WHO

807 recommendations on use of single dose TCVs in endemic settings[219,220]. TCV is well-tolerated
808 and may be co-administered with other childhood vaccines, facilitating its integration into
809 the WHOs Expanded Programme on Immunisation (EPI) at 9–18 months of age. In low
810 resource countries, Gavi (the Vaccine Alliance) will co-finance the introduction of TCV into
811 EPI, and fully finance single dose catch-up campaigns for all children up to 15 years of
812 age[221]. Country introductions have begun in Africa and Asia, however, most at-risk children
813 globally remain without protection. To this end, a coordinated multidisciplinary approach
814 that includes advocacy and communications; country support for decision-making,
815 preparation of Gavi applications and planning of vaccine delivery is essential to ensure that
816 more children are protected from this disease sooner. Additionally, an adequate stable
817 manufactured supply of prequalified vaccine is required to meet country demand.

818 In endemic areas, incorporating TCV into the routine immunisation schedule at 9 months of
819 age with an initial catch-up campaign to 15 years of age has generally been found to be
820 cost-effective[213,222,223]. When factoring in the indirect costs to patients, TCVs may even be
821 cost-saving.[224,225]

822 Two TCVs are prequalified by the WHO and are considered equally effective. Furthermore,
823 several TCVs are approved nationally or are under development[226] . However, as with other
824 conjugate vaccines, robust data on relative effectiveness of different products is important
825 to provide confidence to policymakers on use of different vaccines, highlighting the
826 importance of ongoing impact studies in settings where TCV has been introduced. These
827 studies will inform the long-term TCV strategy.

828 Perhaps the most important outstanding scientific question regarding the global TCV
829 programme is the duration of protection. Although the TCV efficacy trials have shown
830 robust and durable protection against disease (~80 %)for >4 years after vaccination in pre-
831 school and school-age children,[172] long term protection studies are needed for children
832 immunised with a single dose of vaccine at 9–18 months of age in the EPI schedule. Ongoing
833 long-term post-introduction effectiveness and impact studies may strengthen evidence in
834 this domain. Given the high rates of disease reported among school-age children, the need
835 for a booster prior to school entry in those vaccinated in early-life routine immunisation

programmes, must be assessed in Africa and Asia in areas where the vaccine is being rolled out.

The population primarily responsible for transmission of typhoid remains unknown. A cluster-randomised trial in Bangladesh in which children <16 years of age were vaccinated found no evidence of indirect protection. This finding implies that the vaccine either prevents clinical illness but does not prevent transmission, or that adults also contribute substantially to transmission[149,150]. Alternatively, the complexities and biases in a cluster-randomised design in an urban setting might make it impossible to detect herd effects that are present. Such information could help inform whether extending vaccination to older age groups might provide additional population-level benefits. Targeted vaccination of those adults responsible for transmission could possibly improve typhoid control in high-burden settings. Ongoing observational studies in countries implementing TCVs may provide further evidence to address this question in the next 5 years.

Improved diagnostics are needed for clinical management of disease and to define burden and inform decision-making on TCV introduction. Innovation and flexibility is needed to ensure that the most disadvantaged children have access to TCV. Furthermore, without accurate diagnostics, the impact of TCV might be less apparent, for example, in South Asia where incidence of paratyphoid infection is substantial and symptoms are indistinguishable from typhoid. Developments in paratyphoid vaccines, combined with TCV, could broaden protection if shown to be effective and reduce the overall enteric fever burden further. With ongoing early safety and immunogenicity studies of bivalent typhoid and paratyphoid vaccines underway, a combined vaccine could be available within the next 5 years. Furthermore, early phase studies combining TCV with emerging multivalent vaccines against invasive non-typhoidal salmonellae, which could broaden the impact of vaccine programmes are in progress.[227]

Despite the huge progress in protecting children against typhoid, ongoing transmission of salmonella and other bacterial pathogens in affected populations can only be fully controlled with improvements in WASH and food safety. Improving and maintaining WASH requires considerable financing, structural change and political commitment, and some low-income areas have experienced poor sanitation for decades. The impacts of climate change may not only alter the environmental and household patterns of transmission of typhoid,

but also likely heighten the challenge of delivering sustained improvements in WASH. The global rise of antimicrobial resistance further adds relevance and urgency to the importance of vaccines. The sparsity of new antimicrobials in development also underscores the need for mobilising all available means of control. The remarkable efforts in typhoid immunisation programmes will help protect at-risk children in the face of these global challenges.

Tables

Table 1: Case Definitions for typhoid fever disease states

Condition	Definition
Acute typhoid fever	Laboratory confirmation by culture or molecular methods of *S*. Typhi or detection of S. Typhi DNA from a normally sterile site.
Relapse of typhoid fever	Laboratory confirmation of *S*. Typhi from a normally sterile site within one month of completing an appropriate course of antimicrobial treatment and resolution of symptoms.
Chronic typhoid carrier	Evidence of shedding of *S*. Typhi (positive stool culture or PCR) at least 12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease or Two stool samples 12 months apart positive for *S.* Typhi.
Convalescent Carrier	Evidence of shedding *S*. Typhi (positive stool culture or PCR) 1–12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease
Suspected case of typhoid	Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area or Fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid fever

Adapted with permission from ref [2], World Health Organisation.

878 **Table 2: Summary of efficacy and effectiveness estimates for TCV.**

Country	Design	Control vaccine	Age	Study period	Duration of follow-up	Number enrolled	Efficacy (95% CI)	Refs
Malawi efficacy	Individually-randomized	MCV-A	9 months–12 years	Feb 2018–Apr 2020	18-24 months	28,130	80.7% (64.2–89.6)	[168]
				Feb 2018–Sept 2022	4.3 years		78.0% (66.3–86.1)	[172]
Nepal efficacy	Individually-randomized	MCV-A	9 months–15 years	Nov 2017–Apr 2018	12 months	20,019	81.6% (58.8–91.8)	[171]
				Nov 2017–Feb 2020	24 months		79.0% (61.9–88.5)	[228]
Bangladesh efficacy	Cluster-randomized	JE (SA 14-14-2)	9 months–16 years	Apr 2018–May 2020	17.1 months	~ 67,500	Total protection 81% (39–94.0%) Overall protection 56% (43–68.0) Indirect protection 19% (-12–41)	[174]
India Effectiveness	Cluster-randomized Test Negative	NA	9 months-14 years	Sept 2018–Mar 2021	31 months	NA	Programmatic overall effectiveness 56% (25–74)	[176]
Pakistan Effectiveness	Cohort	NA	6 months–10 years	Feb 2018–Dec 2019	23 months	NA	Culture confirmed *S.* Typhi 95.0% (93.0% to 96.0%) XDR S. Typhi 97.0% (95.0% to 98.0)	[229]
Zimbabwe Effectiveness	Case–control	NA	6months–15 years	July 2019–March 2020	9 months	NA	84% (57–94)	[178]

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Boxes

Box 1: Accelerating vaccine testing with CHIM.

Besides improving our understanding of disease pathogenesis, the CHIM also provides a controlled method for testing novel vaccines at a lower cost and greater speed than large-scale traditional field trials. The Oxford CHIM has performed two such trials.

[b1] M01ZH09 vaccine

The CHIM model was used to study the efficacy of an oral live attenuated vaccine, M01ZH09 — designed by deleting *ssaV* and *aroC*[230] . The vaccine did not meet significance for protective efficacybut induced strong antibody responses against lipopolysaccharide, which were bactericidal. The antibodies were not associated with protection against infection; however, the vaccinees demonstrated lower severity of symptoms, delayed onset of infection and a lower level of bacteraemia than non-vaccinees[230]. Similarly, vaccination of individuals with Vi-polysaccharide-containing vaccines induced bactericidal antibodies, but these functional antibodies were not associated with protection from infection when these individuals were challenged with *S.* Typhi[231]. Duration of bacteraemia with the antibiotic-susceptible strain was longer when treated with azithromycin than ciprofloxacin[232].

[b2] Typhoid conjugate vaccine

A multi-arm phase 2b study comparing a novel TCV and a WHO pre-qualified and licensed Vi-polysaccharide (Vi-PS) vaccine against a control vaccine (one that has no protective efficacy against *S.* Typhi) showed that the TCV had comparable efficacy to the existing Vi-PS vaccine in the model[164]. Extensive analysis of class, subclass, avidity and functional serological responses showed that Vi IgA levels and avidity associated with protection from *S.* Typhi challenge, and increased anti-Vi IgG responses were associated with reduced symptoms. In addition, antibody-dependent neutrophil phagocytosis was also associated with protection[233,234]. Vaccination with TCV induced α4β7 and CCR10a^{+}IgA^{+} plasma cells indicating likely mucosal migration, which may be important as this is the site of invasion if there is a future exposure to the organism. Moreover, in those who received TCV, protection against infection was associated with the total plasma cell response[235].

Box 2: Patient experience

[Au: To be able to publish these testimonials, we need to know whether you have received written informed consent from the patients for the statement to be used in this way. We don't need to see the consent forms to not breach confidentiality – we just need you to confirm that you have the consent. We cannot publish these statements if we are not sure that you have written informed consent as stated in our policies:
https://www.nature.com/nrdp/editorial-policies#patient
Please confirm.]

Bashir's experience with typhoid

I am a 10-year-old boy from Badin, Sindh province, Pakistan. My ten siblings and I have never been to school. My father is a vegetable seller and earns about three to four dollars a day – which is only enough for two meals – so we stay at home, helping him with his work or playing with friends.

One day, while playing cricket, I found I had little energy to run. I returned home and told my mother that I was feeling unwell. I rested in bed for days, but my temperature kept increasing. My father took me to a nearby doctor who gave me medication and charged us six dollars. Even with the medication my body was still burning like an oven. I went to another doctor, who gave me a blood test and diagnosed me with typhoid. He charged us 27 dollars and prescribed more medication. After taking it, my condition continued to worsen. I began vomiting, feeling pain in my stomach, and was unable to even take a sip of water.

I was taken to a hospital in Badin, despite my family not having money for transportation or hospital care. There, I was told my intestine had burst and only a major surgery could save my life. We did not have the money for this procedure. I cried while thinking my life was about to end. An ambulance driver, who I think may be a guardian angel, suggested we travel to the National Institute of Child Health in Karachi, where patients are treated at almost no cost.

Accompanied by my family, we reached Karachi via ambulance and paid $45 for the four-hour journey. I underwent surgery the same night and began my recovery. I feel like I have been given another chance at life.

Figure legends

Figure 1. Global incidence of typhoid fever.
Incidence rates per 100,000 person-years of observation for typhoid fever, by country, in 2019. Highest incidence areas are shown in red, and low incidence areas in blue.
Reprinted with permission from Ref [32], The Institute for Health Metrics and Evaluation.

Figure 2: Salmonella Typhi genotype prevalence by world region.
This figure demonstrates the prevalence of genotypes of S. Typhi across the world. Countries contributing data are shaded in beige, and are grouped by regions as defined by the UN statistics division. These data are based on assumed acute cases isolated from untargeted sampling frames from 2010 until 2020, with known country of origin (total N=9,478 genomes).
Adapted from ref [57], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Figure 3: Pathogenesis of typhoid fever following pathogen ingestion.
A schematic figure relating the clinical presentation of typhoid fever to stages of disease pathogenesis. Ingestion of *S*. Typhi and invasion across gut wall are typically asymptomatic with an incubation period of 5-7 days. Following primary dissemination in lymph and blood, a deep-seated systemic reticuloendothelial infection is established and presents with secondary bacteraemia and high fever. Complications include metastatic focal tissue infections. Colonisation of the gallbladder by *S.* Typhi, and excretion of bacteria back into the gastrointestinal tract in infected bile is a hallmark of typhoid, and is the basis for long-term chronic carrier state and transmission. Re-infection of Peyer's patches from the lumen may result in gastrointestinal bleeding or intestinal perforation caused by necrotic Peyer's patches. Intestinal perforation may also result in a tertiary blood stream infection with a range of gut luminal enteric organisms. .

Figure 4: Clinical signs and symptoms of typhoid fever.
Typhoid fever presents predominantly with fever, headache and abdominal pain, but symptoms and signs can be heterogenous and can include all organ systems.

REFERENCES

1 Dougan, G. & Baker, S. Salmonella enterica Serovar Typhi and the Pathogenesis of Typhoid Fever. *Annual Review of Microbiology* **68**, 317-336, doi:10.1146/annurev-micro-091313-103739 (2014).

2 Organisation, W. H. *Typhoid: Vaccine Preventable Diseases Surveillance Standards*, <https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-typhoid> (2018).

3 Basnyat, B., Qamar, F. N., Rupali, P., Ahmed, T. & Parry, C. M. Enteric fever. *Bmj* **372**, n437, doi:10.1136/bmj.n437 (2021).

4 Von Drigalski, K. W. *Ueber Ergebnisse bei der Bekämpfung des Typhus nach Robert Koch*. (1904).

5 Kirchhelle, C., Pollard, A. J. & Vanderslott, S. Typhoid-From Past to Future. *Clin Infect Dis* **69**, S375-s376, doi:10.1093/cid/ciz551 (2019).

6 Ames, W. R. & Robins, M. Age and Sex as Factors in the Development of the Typhoid Carrier State, and a Method for Estimating Carrier Prevalence. *Am J Public Health Nations Health* **33**, 221-230, doi:10.2105/ajph.33.3.221 (1943).

7 Antillon, M., Saad, N. J., Baker, S., Pollard, A. J. & Pitzer, V. E. The Relationship Between Blood Sample Volume and Diagnostic Sensitivity of Blood Culture for Typhoid and Paratyphoid Fever: A Systematic Review and Meta-Analysis. *J Infect Dis* **218**, S255-s267, doi:10.1093/infdis/jiy471 (2018).

8 Nizamuddin, S., Khan, E. A., Chattaway, M. A. & Godbole, G. Case of Carbapenem-Resistant Salmonella Typhi Infection, Pakistan, 2022. *Emerging Infectious Disease journal* **29**, doi:10.3201/eid2911.230499 (2023).

9 Phillips, M. T., Owers, K. A., Grenfell, B. T. & Pitzer, V. E. Changes in historical typhoid transmission across 16 U.S. cities, 1889-1931: Quantifying the impact of investments in water and sewer infrastructures. *PLoS Negl Trop Dis* **14**, e0008048, doi:10.1371/journal.pntd.0008048 (2020).

10 Vanderslott, S., Phillips, M. T., Pitzer, V. E. & Kirchhelle, C. Water and Filth: Reevaluating the First Era of Sanitary Typhoid Intervention (1840-1940). *Clin Infect Dis* **69**, S377-s384, doi:10.1093/cid/ciz610 (2019).

11 Stanaway, J. D. *et al.* The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Infectious Diseases* **19**, doi:10.1016/S1473-3099(18)30685-6 (2019).

12 Crump, J. A. Progress in Typhoid Fever Epidemiology. *Clin Infect Dis* **68**, S4-s9, doi:10.1093/cid/ciy846 (2019).

13 Appiah, G. D. *et al.* Typhoid Outbreaks, 1989-2018: Implications for Prevention and Control. *Am J Trop Med Hyg* **102**, 1296-1305, doi:10.4269/ajtmh.19-0624 (2020).

14 Reller, M. E. *et al.* in *39th Annual Meeting of the Infectious Diseases Society of America.* (ed IDSA) 199 (Infectious Diseases Society of America, Alexandria, VA).

15 Mitscherlich, E. & Marth, E. H. in *Microbial survival in the environment* (eds E. Mitscherlich & E.H. Marth) 1-560 (Springer, 1984).

16 Cho, J.-C. & Kim, S. J. Viable, but non-culturable, state of a green fluorescence protein-tagged environmental isolate of *Salmonella* Typhi in groundwater and pond water. *FEMS Microbiol Lett* **170**, 257-264 (1999).

17 Kingsley, R. A. *et al.* Functional analysis of *Salmonella* Typhi adaptation to survival in water. *Environ Microbiol* **20**, 4079-4090 (2018).
18 Andrews, J. R. *et al.* Environmental surveillance as a tool for identifying high-risk settings for typhoid transmission. *Clin Infect Dis* **71 (suppl 2)**, S71-S78 (2020).
19 Deen, J. *et al.* Community-acquired bacterial bloodstream infections in developing countries in south and southeast Asia: a systematic review. *Lancet Infect Dis* **12**, 480-487 (2012).
20 Reddy, E. A., Shaw, A. V. & Crump, J. A. Community acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infect Dis* **10**, 417-432 (2010).
21 Marchello, C. S., Dale, A. P., Pisharody, S., Rubach, M. P. & Crump, J. A. Prevalence of community-onset bloodstream infections among hospitalized patients in Africa and Asia: a systematic review and meta-analysis. *Antimicrobial agents and chemotherapy* **64**, e01974-01919 (2019).
22 Garrett, D. O. *et al.* Incidence of typhoid and paratyphoid fever in Bangladesh, Nepal, and Pakistan: results of the Surveillance for Enteric Fever in Asia Project. *Lancet Glob Health* **10**, e978-988 (2022).
23 Marks, F. *et al.* The Severe Typhoid in Africa Program: incidences of typhoid fever in Burkina Faso, Democratic Republic of Congo, Ethiopia, Ghana, Madagascar, and Nigeria. Available at SSRN: https://ssrn.com/abstract=4292849 or http://dx.doi.org/4292810.4292139/ssrn.4292849 (2022).
24 Marks, F. *et al.* Incidence of invasive *Salmonella* disease in sub-Saharan Africa: a multicentre population-based surveillance study. *Lancet Glob Health* **5**, e310-323 (2017).
25 Meiring JE, e. a. Burden of enteric fever at three urban sites in Africa and Asia: a multicentre population-based study with 626,219 person-years of observation. *Lancet Glob Hlth* (2021).
26 John, J. *et al.* Burden of Typhoid and Paratyphoid Fever in India. *New England Journal of Medicine* **388**, 1491-1500, doi:10.1056/NEJMoa2209449 (2023).
27 Crump, J. A., Luby, S. P. & Mintz, E. D. The global burden of typhoid fever. *Bull World Health Organ* **82**, 346-353 (2004).
28 Antillón, M. *et al.* The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. *PLoS Negl Trop Dis* **11**, e0005376 (2017).
29 Mogasale, V. *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* **2**, e570-580 (2014).
30 Buckle, G. C., Walker, C. L. & Black, R. E. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. *J Glob Health* **2**, 10401 (2012).
31 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* **19**, 369-381 (2019).
32 Evaluation, I. f. H. M. a. *Global Incidence of Typhoid Fever*, <https://vizhub.healthdata.org/gbd-compare/> (2019).
33 Crump, J. A. & Kirk, M. D. Estimating the burden of febrile illnesses. *PLoS Negl Trop Dis* **9**, e0004040 (2015).

34 Marchello, C. S., Hong, C. Y. & Crump, J. A. Global typhoid fever incidence: a systematic review and meta-analysis. *Clin Infect Dis* **68 (suppl 2)**, S105-S116 (2019).

35 Crump, J. A. *et al.* Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. *Emerg Infect Dis* **9**, 539-544, doi:10.3201/eid0905.020428 (2003).

36 Marchello, C. S., Birkhold, M. & Crump, J. A. Complications and mortality of typhoid fever: A global systematic review and meta-analysis. *J Infect* **81**, 902-910, doi:10.1016/j.jinf.2020.10.030 (2020).

37 Marchello, C. S., Birkhold, M. & Crump, J. A. Complications and mortality of typhoid fever: A global systematic review and meta-analysis. *J Infect* **81**, 902-910 (2020).

38 Gibani, M. M. *et al.* Homologous and heterologous re-challenge with Salmonella Typhi and Salmonella Paratyphi A in a randomised controlled human infection model. *PLoS Negl Trop Dis* **14**, e0008783, doi:10.1371/journal.pntd.0008783 (2020).

39 Im, J. *et al.* Protection conferred by typhoid fever against recurrent typhoid fever in urban Kolkata. *PLoS Negl Trop Dis* **14**, e0008530, doi:10.1371/journal.pntd.0008530 (2020).

40 Brockett, S. *et al.* Associations among water, sanitation, and hygiene, and food exposures and typhoid fever in case-control studies: a systematic review and meta-analysis. *Am J Trop Med Hyg* **103**, 1020-1031 (2020).

41 Tadesse, B. T. *et al.* Prevention of typhoid by Vi conjugate vaccine and achievable improvements in household water, sanitation, and hygiene: evidence from a cluster-randomized trial in Dhaka, Bangladesh. *Clin Infect Dis* **75**, 1681-1687 (2022).

42 Gunn, J. S. *et al.* Salmonella chronic carriage: epidemiology, diagnosis, and gallbladder persistence. *Trends Microbiol* **22**, 648-655, doi:10.1016/j.tim.2014.06.007 (2014).

43 Dunstan, S. J. *et al.* Variation at HLA-DRB1 is associated with resistance to enteric fever. *Nat Genet* **46**, 1333-1336 (2014).

44 Saad, N. J. *et al.* Seasonal dynamics of typhoid and paratyphoid fever. *Sci Rep* **8**, 6870 (2018).

45 Thindwa, D., Chipeta, M. G., Henrion, M. Y. R. & Gordon, M. A. Distinct climate influences on the risk of typhoid compared to invasive non-typhoid Salmonella disease in Blantyre, Malawi. *Sci Rep* **9**, 20310, doi:10.1038/s41598-019-56688-1 (2019).

46 Levy, K., Smith, S. M. & Carlton, E. J. Climate Change Impacts on Waterborne Diseases: Moving Toward Designing Interventions. *Curr Environ Health Rep* **5**, 272-282, doi:10.1007/s40572-018-0199-7 (2018).

47 Gao, Q. *et al.* Impact of Temperature and Rainfall on Typhoid/Paratyphoid Fever in Taizhou, China: Effect Estimation and Vulnerable Group Identification. *Am J Trop Med Hyg* **106**, 532-542, doi:10.4269/ajtmh.20-1457 (2021).

48 Hickman-Brenner, F. W. & Farmer, J. J., 3rd. Bacteriophage types of Salmonella typhi in the United States from 1974 through 1981. *J Clin Microbiol* **17**, 172-174, doi:10.1128/jcm.17.1.172-174.1983 (1983).

49 Chattaway, M. A., Langridge, G. C. & Wain, J. Salmonella nomenclature in the genomic era: a time for change. *Sci Rep* **11**, 7494, doi:10.1038/s41598-021-86243-w (2021).

50 Wong, V. K. *et al.* Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. *Nat Genet* **47**, 632-639, doi:10.1038/ng.3281 (2015).
51 Tanmoy, A. M. *et al.* Paratype: a genotyping tool for Salmonella Paratyphi A reveals its global genomic diversity. *Nature Communications* **13**, 7912, doi:10.1038/s41467-022-35587-6 (2022).
52 Kariuki, S. *et al.* Multiple introductions of multidrug-resistant typhoid associated with acute infection and asymptomatic carriage, Kenya. *Elife* **10**, doi:10.7554/eLife.67852 (2021).
53 Dyson, Z. A. *et al.* Genomic epidemiology and antimicrobial resistance transmission of Salmonella Typhi and Paratyphi A at three urban sites in Africa and Asia. *medRxiv*, 2023.2003.2011.23286741, doi:10.1101/2023.03.11.23286741 (2023).
54 Wong, V. K. *et al.* An extended genotyping framework for Salmonella enterica serovar Typhi, the cause of human typhoid. *Nature Communications* **7**, 12827, doi:10.1038/ncomms12827 (2016).
55 Dyson, Z. A. & Holt, K. E. Five Years of GenoTyphi: Updates to the Global Salmonella Typhi Genotyping Framework. *The Journal of Infectious Diseases* **224**, S775-S780, doi:10.1093/infdis/jiab414 (2021).
56 Carey, M. E. *et al.* Global diversity and antimicrobial resistance of typhoid fever pathogens: Insights from a meta-analysis of 13,000 Salmonella Typhi genomes. *eLife* **12**, e85867, doi:10.7554/eLife.85867 (2023).
57 Carey, M. E. *et al.* Global diversity and antimicrobial resistance of typhoid fever pathogens: insights from 13,000 Salmonella Typhi genomes. *medRxiv*, 2022.2012.2028.22283969, doi:10.1101/2022.12.28.22283969 (2022).
58 da Silva, K. E. *et al.* The international and intercontinental spread and expansion of antimicrobial-resistant Salmonella Typhi: a genomic epidemiology study. *Lancet Microbe* **3**, e567-e577, doi:10.1016/s2666-5247(22)00093-3 (2022).
59 Park, S. E. *et al.* The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa. *Nat Commun* **9**, 5094, doi:10.1038/s41467-018-07370-z (2018).
60 Guevara, P. D. *et al.* A genomic snapshot of Salmonella enterica serovar Typhi in Colombia. *PLoS Negl Trop Dis* **15**, e0009755, doi:10.1371/journal.pntd.0009755 (2021).
61 Maes, M. *et al.* Whole genome sequence analysis of Salmonella Typhi provides evidence of phylogenetic linkage between cases of typhoid fever in Santiago, Chile in the 1980s and 2010–2016. *PLOS Neglected Tropical Diseases* **16**, e0010178, doi:10.1371/journal.pntd.0010178 (2022).
62 Sikorski, M. J. *et al.* Persistence of Rare Salmonella Typhi Genotypes Susceptible to First-Line Antibiotics in the Remote Islands of Samoa. *mBio*, e0192022, doi:10.1128/mbio.01920-22 (2022).
63 Davies, M. R. *et al.* Genomic epidemiology of Salmonella Typhi in Central Division, Fiji, 2012 to 2016. *Lancet Reg Health West Pac* **24**, 100488, doi:10.1016/j.lanwpc.2022.100488 (2022).
64 Wirth, T. Massive lineage replacements and cryptic outbreaks of Salmonella Typhi in eastern and southern Africa. *Nat Genet* **47**, 565-567, doi:10.1038/ng.3318 (2015).

65 Gibani, M. M., Britto, C. & Pollard, A. J. Typhoid and paratyphoid fever: a call to action. *Curr Opin Infect Dis*, doi:10.1097/qco.0000000000000479 (2018).
66 Johnson, R., Mylona, E. & Frankel, G. Typhoidal Salmonella: Distinctive virulence factors and pathogenesis. *Cell Microbiol* **20**, e12939, doi:10.1111/cmi.12939 (2018).
67 McClelland, M. *et al.* Comparison of genome degradation in Paratyphi A and Typhi, human-restricted serovars of Salmonella enterica that cause typhoid. *Nat Genet* **36**, 1268-1274, doi:10.1038/ng1470 (2004).
68 Parkhill, J. *et al.* Complete genome sequence of a multiple drug resistant Salmonella enterica serovar Typhi CT18. *Nature* **413**, 848-852, doi:10.1038/35101607 (2001).
69 Holt, K. E. *et al.* High-throughput bacterial SNP typing identifies distinct clusters of Salmonella Typhi causing typhoid in Nepalese children. *BMC Infect Dis* **10**, 144, doi:10.1186/1471-2334-10-144 (2010).
70 Hiyoshi, H., Tiffany, C. R., Bronner, D. N. & Bäumler, A. J. Typhoidal Salmonella serovars: ecological opportunity and the evolution of a new pathovar. *FEMS Microbiol Rev* **42**, 527-541, doi:10.1093/femsre/fuy024 (2018).
71 Rogers, A. W. L., Tsolis, R. M. & Bäumler, A. J. Salmonella versus the Microbiome. *Microbiol Mol Biol Rev* **85**, doi:10.1128/mmbr.00027-19 (2021).
72 Bronner, D. N. *et al.* Genetic Ablation of Butyrate Utilization Attenuates Gastrointestinal Salmonella Disease. *Cell Host Microbe* **23**, 266-273.e264, doi:10.1016/j.chom.2018.01.004 (2018).
73 Winter, S. E. *et al.* The flagellar regulator TviA reduces pyroptosis by Salmonella enterica serovar Typhi. *Infect Immun* **83**, 1546-1555, doi:10.1128/iai.02803-14 (2015).
74 Pickard, D. *et al.* Composition, acquisition, and distribution of the Vi exopolysaccharide-encoding Salmonella enterica pathogenicity island SPI-7. *J Bacteriol* **185**, 5055-5065, doi:10.1128/jb.185.17.5055-5065.2003 (2003).
75 Ménard, S. *et al.* Cross-Talk Between the Intestinal Epithelium and Salmonella Typhimurium. *Front Microbiol* **13**, 906238, doi:10.3389/fmicb.2022.906238 (2022).
76 Dillon, A. & Lo, D. D. M Cells: Intelligent Engineering of Mucosal Immune Surveillance. *Frontiers in Immunology* **10**, doi:10.3389/fimmu.2019.01499 (2019).
77 Watson, K. G. & Holden, D. W. Dynamics of growth and dissemination of Salmonella in vivo. *Cell Microbiol* **12**, 1389-1397, doi:10.1111/j.1462-5822.2010.01511.x (2010).
78 Hart, P. J. *et al.* Differential Killing of Salmonella enterica Serovar Typhi by Antibodies Targeting Vi and Lipopolysaccharide O:9 Antigen. *PLoS One* **11**, e0145945, doi:10.1371/journal.pone.0145945 (2016).
79 Waddington, C. S. *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* **58**, 1230-1240, doi:10.1093/cid/ciu078 (2014).
80 Waddington, C. S. *et al.* Advancing the management and control of typhoid fever: a review of the historical role of human challenge studies. *J Infect* **68**, 405-418, doi:10.1016/j.jinf.2014.01.006 (2014).

81 Dobinson, H. C. *et al.* Evaluation of the Clinical and Microbiological Response to Salmonella Paratyphi A Infection in the First Paratyphoid Human Challenge Model. *Clin Infect Dis* **64**, 1066-1073, doi:10.1093/cid/cix042 (2017).
82 Darton, T. C. *et al.* Blood culture-PCR to optimise typhoid fever diagnosis after controlled human infection identifies frequent asymptomatic cases and evidence of primary bacteraemia. *J Infect* **74**, 358-366, doi:10.1016/j.jinf.2017.01.006 (2017).
83 Blohmke, C. J. *et al.* Interferon-driven alterations of the host's amino acid metabolism in the pathogenesis of typhoid fever. *The Journal of Experimental Medicine* **213**, 1061-1077, doi:10.1084/jem.20151025 (2016).
84 Darton, T. C. *et al.* Rapidly Escalating Hepcidin and Associated Serum Iron Starvation Are Features of the Acute Response to Typhoid Infection in Humans. *PLoS Negl Trop Dis* **9**, e0004029, doi:10.1371/journal.pntd.0004029 (2015).
85 Darton, T. C. *et al.* Identification of Novel Serodiagnostic Signatures of Typhoid Fever Using a Salmonella Proteome Array. *Front Microbiol* **8**, 1794, doi:10.3389/fmicb.2017.01794 (2017).
86 Blohmke, C. J. *et al.* Diagnostic host gene signature for distinguishing enteric fever from other febrile diseases. *EMBO Mol Med* **11**, e10431, doi:10.15252/emmm.201910431 (2019).
87 Song, J., Gao, X. & Galán, J. E. Structure and function of the Salmonella Typhi chimaeric A(2)B(5) typhoid toxin. *Nature* **499**, 350-354, doi:10.1038/nature12377 (2013).
88 Del Bel Belluz, L. *et al.* The Typhoid Toxin Promotes Host Survival and the Establishment of a Persistent Asymptomatic Infection. *PLoS Pathog* **12**, e1005528, doi:10.1371/journal.ppat.1005528 (2016).
89 den Bakker, H. C. *et al.* Genome sequencing reveals diversification of virulence factor content and possible host adaptation in distinct subpopulations of Salmonella enterica. *BMC Genomics* **12**, 425, doi:10.1186/1471-2164-12-425 (2011).
90 Rodriguez-Rivera, L. D., Bowen, B. M., den Bakker, H. C., Duhamel, G. E. & Wiedmann, M. Characterization of the cytolethal distending toxin (typhoid toxin) in non-typhoidal Salmonella serovars. *Gut Pathog* **7**, 19, doi:10.1186/s13099-015-0065-1 (2015).
91 Gibani, M. M. *et al.* Investigation of the role of typhoid toxin in acute typhoid fever in a human challenge model. *Nat Med* **25**, 1082-1088, doi:10.1038/s41591-019-0505-4 (2019).
92 Pitzer, V. E. *et al.* Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: a mathematical modeling study. *PLoS Negl Trop Dis* **8**, e2642, doi:10.1371/journal.pntd.0002642 (2014).
93 Saul, A., Smith, T. & Maire, N. Stochastic simulation of endemic Salmonella enterica serovar Typhi: the importance of long lasting immunity and the carrier state. *PLoS One* **8**, e74097, doi:10.1371/journal.pone.0074097 (2013).
94 Gibani, M. M. *et al.* The Impact of Vaccination and Prior Exposure on Stool Shedding of Salmonella Typhi and Salmonella Paratyphi in 6 Controlled Human Infection Studies. *Clin Infect Dis* **68**, 1265-1273, doi:10.1093/cid/ciy670 (2019).
95 Marchello, C. S., Carr, S. D. & Crump, J. A. A Systematic Review on Antimicrobial Resistance among Salmonella Typhi Worldwide. *Am J Trop Med Hyg*, doi:10.4269/ajtmh.20-0258 (2020).

96 Britto, C. D., Wong, V. K., Dougan, G. & Pollard, A. J. A systematic review of antimicrobial resistance in Salmonella enterica serovar Typhi, the etiological agent of typhoid. *PLoS Negl Trop Dis* **12**, e0006779, doi:10.1371/journal.pntd.0006779 (2018).
97 Bowe, F. *et al.* At least four percent of the Salmonella typhimurium genome is required for fatal infection of mice. *Infect Immun* **66**, 3372-3377, doi:10.1128/iai.66.7.3372-3377.1998 (1998).
98 Chau, T. T. *et al.* Antimicrobial drug resistance of Salmonella enterica serovar typhi in asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. *Antimicrobial agents and chemotherapy* **51**, 4315-4323, doi:10.1128/aac.00294-07 (2007).
99 Day, M. R. *et al.* Comparison of phenotypic and WGS-derived antimicrobial resistance profiles of Salmonella enterica serovars Typhi and Paratyphi. *J Antimicrob Chemother* **73**, 365-372, doi:10.1093/jac/dkx379 (2018).
100 Qamar, F. N. *et al.* Antimicrobial Resistance in Typhoidal Salmonella: Surveillance for Enteric Fever in Asia Project, 2016-2019. *Clin Infect Dis* **71**, S276-s284, doi:10.1093/cid/ciaa1323 (2020).
101 Akram, J. *et al.* Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management. *Biomed Res Int* **2020**, 6432580, doi:10.1155/2020/6432580 (2020).
102 Posen, H. J. *et al.* Travel-associated extensively drug-resistant typhoid fever: a case series to inform management in non-endemic regions. *J Travel Med* **30**, doi:10.1093/jtm/taac086 (2023).
103 Herdman, M. T. *et al.* Increasingly limited options for the treatment of enteric fever in travellers returning to England, 2014-2019: a cross-sectional analytical study. *J Med Microbiol* **70**, doi:10.1099/jmm.0.001359 (2021).
104 Ashton, P. M. *et al.* The rapid emergence of Salmonella Typhi with decreased ciprofloxacin susceptibility following an increase in ciprofloxacin prescriptions in Blantyre, Malawi. *medRxiv*, 2023.2003.2027.23287794, doi:10.1101/2023.03.27.23287794 (2023).
105 Wijedoru, L., Mallett, S. & Parry, C. M. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Rev* **5**, Cd008892, doi:10.1002/14651858.CD008892.pub2 (2017).
106 Azmatullah, A., Qamar, F. N., Thaver, D., Zaidi, A. K. & Bhutta, Z. A. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. *J Glob Health* **5**, 020407, doi:10.7189/jogh.05.020407 (2015).
107 Aiemjoy, K. *et al.* Diagnostic Value of Clinical Features to Distinguish Enteric Fever From Other Febrile Illnesses in Bangladesh, Nepal, and Pakistan. *Clin Infect Dis* **71**, S257-s265, doi:10.1093/cid/ciaa1297 (2020).
108 Andrews, J. R. *et al.* High Rates of Enteric Fever Diagnosis and Lower Burden of Culture-Confirmed Disease in Peri-urban and Rural Nepal. *J Infect Dis* **218**, S214-s221, doi:10.1093/infdis/jix221 (2018).
109 Wain, J. *et al.* Quantitation of bacteria in blood of typhoid fever patients and relationship between counts and clinical features, transmissibility, and antibiotic resistance. *J Clin Microbiol* **36**, 1683-1687, doi:10.1128/jcm.36.6.1683-1687.1998 (1998).
110 Gilman, R. H., Terminel, M., Levine, M. M., Hernandez-Mendoza, P. & Hornick, R. B. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. *Lancet* **1**, 1211-1213, doi:10.1016/s0140-6736(75)92194-7 (1975).

111 Mogasale, V., Ramani, E., Mogasale, V. V. & Park, J. What proportion of Salmonella Typhi cases are detected by blood culture? A systematic literature review. *Ann Clin Microbiol Antimicrob* **15**, 32, doi:10.1186/s12941-016-0147-z (2016).
112 Wain, J. *et al.* Specimens and culture media for the laboratory diagnosis of typhoid fever. *J Infect Dev Ctries* **2**, 469-474, doi:10.3855/jidc.164 (2008).
113 Neupane, D. P., Dulal, H. P. & Song, J. Enteric Fever Diagnosis: Current Challenges and Future Directions. *Pathogens* **10**, doi:10.3390/pathogens10040410 (2021).
114 Tennant, S. M. *et al.* Detection of Typhoidal and Paratyphoidal Salmonella in Blood by Real-time Polymerase Chain Reaction. *Clin Infect Dis* **61 Suppl 4**, S241-250, doi:10.1093/cid/civ726 (2015).
115 Sapkota, J. *et al.* Comparative Analysis of Commercially Available Typhoid Point-of-Care Tests: Results of a Prospective and Hybrid Retrospective Multicenter Diagnostic Accuracy Study in Kenya and Pakistan. *J Clin Microbiol* **60**, e0100022, doi:10.1128/jcm.01000-22 (2022).
116 Charles, R. C. *et al.* Immunoproteomic analysis of antibody in lymphocyte supernatant in patients with typhoid fever in Bangladesh. *Clin Vaccine Immunol* **21**, 280-285, doi:10.1128/cvi.00661-13 (2014).
117 Liang, L. *et al.* Immune profiling with a Salmonella Typhi antigen microarray identifies new diagnostic biomarkers of human typhoid. *Sci Rep* **3**, 1043, doi:10.1038/srep01043 (2013).
118 Andrews, J. R. *et al.* Plasma Immunoglobulin A Responses Against 2 Salmonella Typhi Antigens Identify Patients With Typhoid Fever. *Clin Infect Dis* **68**, 949-955, doi:10.1093/cid/ciy578 (2019).
119 Näsström, E. *et al.* Reproducible diagnostic metabolites in plasma from typhoid fever patients in Asia and Africa. *eLife* **6**, e15651, doi:10.7554/eLife.15651 (2017).
120 Aiemjoy, K. *et al.* Estimating typhoid incidence from community-based serosurveys: a multicohort study. *Lancet Microbe* **3**, e578-e587, doi:10.1016/s2666-5247(22)00114-8 (2022).
121 Mylona, E. *et al.* The Identification of Enteric Fever-Specific Antigens for Population-Based Serosurveillance. *The Journal of Infectious Diseases*, doi:10.1093/infdis/jiad242 (2023).
122 Parry, C. M., Hien, T. T., Dougan, G., White, N. J. & Farrar, J. J. Typhoid fever. *N Engl J Med* **347**, 1770-1782, doi:10.1056/NEJMra020201 (2002).
123 Stuart, B. M. & Pullen, R. L. Typhoid; clinical analysis of 360 cases. *Arch Intern Med (Chic)* **78**, 629-661, doi:10.1001/archinte.1946.00220060002001 (1946).
124 Crump, J. A., Sjölund-Karlsson, M., Gordon, M. A. & Parry, C. M. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. *Clin Microbiol Rev* **28**, 901-937, doi:10.1128/cmr.00002-15 (2015).
125 Hosoglu, S. *et al.* Risk factors for enteric perforation in patients with typhoid Fever. *Am J Epidemiol* **160**, 46-50, doi:10.1093/aje/kwh172 (2004).
126 Birkhold, M. *et al.* Morbidity and mortality of typhoid intestinal perforation among children in sub-Saharan Africa 1995-2019: A scoping review. *World J Surg*, 1-11, doi:10.1007/s00268-020-05567-2 (2020).

127 Neil, K. P. *et al.* A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008-2009. *Clin Infect Dis* **54**, 1091-1099, doi:10.1093/cid/cis025 (2012).
128 Mogasale, V. *et al.* Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: A systematic literature review. *PLoS ONE* **9**, doi:10.1371/journal.pone.0093784 (2014).
129 Osuntokun, B. O., Bademosi, O., Ogunremi, K. & Wright, S. G. Neuropsychiatric manifestations of typhoid fever in 959 patients. *Arch Neurol* **27**, 7-13, doi:10.1001/archneur.1972.00490130009002 (1972).
130 Lutterloh, E. *et al.* Multidrug-resistant typhoid fever with neurologic findings on the Malawi-Mozambique border. *Clin Infect Dis* **54**, 1100-1106, doi:10.1093/cid/cis012 (2012).
131 Britto, C. D. *et al.* Laboratory and molecular surveillance of paediatric typhoidal Salmonella in Nepal: Antimicrobial resistance and implications for vaccine policy. *PLoS Negl Trop Dis* **12**, e0006408, doi:10.1371/journal.pntd.0006408 (2018).
132 Britto, C., Pollard, A. J., Voysey, M. & Blohmke, C. J. An Appraisal of the Clinical Features of Pediatric Enteric Fever: Systematic Review and Meta-analysis of the Age-Stratified Disease Occurrence. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* **64**, 1604-1611, doi:10.1093/cid/cix229 (2017).
133 Cruz Espinoza, L. M. *et al.* Occurrence of Typhoid Fever Complications and Their Relation to Duration of Illness Preceding Hospitalization: A Systematic Literature Review and Meta-analysis. *Clinical Infectious Diseases* **69**, doi:10.1093/cid/ciz477 (2019).
134 Al-Emran, H. M. *et al.* A Multicountry Molecular Analysis of Salmonella enterica Serovar Typhi With Reduced Susceptibility to Ciprofloxacin in Sub-Saharan Africa. *Clin Infect Dis* **62 Suppl 1**, S42-46, doi:10.1093/cid/civ788 (2016).
135 Levine, M. M., Black, R. E. & Lanata, C. Precise estimation of the numbers of chronic carriers of Salmonella typhi in Santiago, Chile, an endemic area. *J Infect Dis* **146**, 724-726, doi:10.1093/infdis/146.6.724 (1982).
136 Khatri, N. S. *et al.* Gallbladder carriage of Salmonella paratyphi A may be an important factor in the increasing incidence of this infection in South Asia. *Ann Intern Med* **150**, 567-568, doi:10.7326/0003-4819-150-8-200904210-00017 (2009).
137 Gonzalez-Escobedo, G., Marshall, J. M. & Gunn, J. S. Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. *Nat Rev Microbiol* **9**, 9-14, doi:10.1038/nrmicro2490 (2011).
138 Crawford, R. W. *et al.* Gallstones play a significant role in Salmonella spp. gallbladder colonization and carriage. *Proc Natl Acad Sci U S A* **107**, 4353-4358, doi:10.1073/pnas.1000862107 (2010).
139 Dongol, S. *et al.* The microbiological and clinical characteristics of invasive salmonella in gallbladders from cholecystectomy patients in kathmandu, Nepal. *PLoS One* **7**, e47342, doi:10.1371/journal.pone.0047342 (2012).
140 Schiøler, H., Christiansen, E. D., Høybye, G., Rasmussen, S. N. & Greibe, J. Biliary calculi in chronic Salmonella carriers and healthy controls: a controlled study. *Scand J Infect Dis* **15**, 17-19, doi:10.3109/inf.1983.15.issue-1.04 (1983).

141 Olsen, S. J. *et al.* Outbreaks of typhoid fever in the United States, 1960-99. *Epidemiol Infect* **130**, 13-21, doi:10.1017/s0950268802007598 (2003).
142 Bokkenheuser, V. DETECTION OF TYPHOID CARRIERS. *Am J Public Health Nations Health* **54**, 477-486, doi:10.2105/ajph.54.3.477 (1964).
143 Avendano, A. *et al.* Duodenal String Cultures: Practicality and Sensitivity for Diagnosing Enteric Fever in Children. *The Journal of Infectious Diseases* **153**, 359-362, doi:10.1093/infdis/153.2.358 (1986).
144 Hoffman, S. A., Sikorski, M. J. & Levine, M. M. Chronic Salmonella Typhi carriage at sites other than the gallbladder. *PLOS Neglected Tropical Diseases* **17**, e0011168, doi:10.1371/journal.pntd.0011168 (2023).
145 Lin, F. Y. *et al.* Restaurant-associated outbreak of typhoid fever in Maryland: identification of carrier facilitated by measurement of serum Vi antibodies. *J Clin Microbiol* **26**, 1194-1197, doi:10.1128/jcm.26.6.1194-1197.1988 (1988).
146 Gupta, A. *et al.* Evaluation of community-based serologic screening for identification of chronic Salmonella typhi carriers in Vietnam. *Int J Infect Dis* **10**, 309-314, doi:10.1016/j.ijid.2005.06.005 (2006).
147 Ferreccio, C. *et al.* [The detection of chronic Salmonella typhi carriers: a practical method applied to food handlers]. *Rev Med Chil* **118**, 33-37 (1990).
148 Lanata, C. F. *et al.* Vi serology in detection of chronic Salmonella typhi carriers in an endemic area. *Lancet* **2**, 441-443, doi:10.1016/s0140-6736(83)90401-4 (1983).
149 Thompson, L. J. *et al.* Transcriptional response in the peripheral blood of patients infected with Salmonella enterica serovar Typhi. *Proc Natl Acad Sci U S A* **106**, 22433-22438, doi:10.1073/pnas.0912386106 (2009).
150 Tran Vu Thieu, N. *et al.* An evaluation of purified Salmonella Typhi protein antigens for the serological diagnosis of acute typhoid fever. *J Infect* **75**, 104-114, doi:10.1016/j.jinf.2017.05.007 (2017).
151 Näsström, E. *et al.* Diagnostic metabolite biomarkers of chronic typhoid carriage. *PLoS Negl Trop Dis* **12**, e0006215, doi:10.1371/journal.pntd.0006215 (2018).
152 Gauld, J. S., Hu, H., Klein, D. J. & Levine, M. M. Typhoid fever in Santiago, Chile: Insights from a mathematical model utilizing venerable archived data from a successful disease control program. *PLOS Neglected Tropical Diseases* **12**, e0006759, doi:10.1371/journal.pntd.0006759 (2018).
153 Ng'eno, E. *et al.* Dynamic Incidence of Typhoid Fever over a 10-Year Period (2010-2019) in Kibera, an Urban Informal Settlement in Nairobi, Kenya. *Am J Trop Med Hyg* **109**, 22-31, doi:10.4269/ajtmh.22-0736 (2023).
154 Sikorski, M. J. & Levine, M. M. Reviving the "Moore Swab": a Classic Environmental Surveillance Tool Involving Filtration of Flowing Surface Water and Sewage Water To Recover Typhoidal Salmonella Bacteria. *Appl Environ Microbiol* **86**, doi:10.1128/aem.00060-20 (2020).
155 Kim, C. *et al.* Associations of water, sanitation, and hygiene with typhoid fever in case-control studies: a systematic review and meta-analysis. *BMC Infect Dis* **23**, 562, doi:10.1186/s12879-023-08452-0 (2023).
156 Stanaway, J. D., Atuhebwe, P. L., Luby, S. P. & Crump, J. A. Assessing the Feasibility of Typhoid Elimination. *Clin Infect Dis* **71**, S179-s184, doi:10.1093/cid/ciaa585 (2020).
157 Hejfec, L. B. RESULTS OF THE STUDY OF TYPHOID VACCINES IN FOUR CONTROLLED FIELD TRIALS IN THE USSR. *Bull World Health Organ* **32**, 1-14 (1965).

158 World Health Organization. Typhoid vaccines: WHO position paper. *Wkly Epidemiol Rec* **83**, 49-59 (2008).
159 Engels, E. A., Falagas, M. E., Lau, J. & Bennish, M. L. Typhoid fever vaccines: a meta-analysis of studies on efficacy and toxicity. *Bmj* **316**, 110-116, doi:10.1136/bmj.316.7125.110 (1998).
160 Milligan, R., Paul, M., Richardson, M. & Neuberger, A. Vaccines for preventing typhoid fever. *Cochrane Database Syst Rev* **5**, Cd001261, doi:10.1002/14651858.CD001261.pub4 (2018).
161 Goldblatt, D. Conjugate vaccines. *Clin Exp Immunol* **119**, 1-3, doi:10.1046/j.1365-2249.2000.01109.x (2000).
162 World Health Organization. Typhoid vaccines: WHO position paper – March 2018. 153-172 (Geneva, Switzerland, 2018).
163 Mohan, V. K. *et al.* Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clin Infect Dis* **61**, 393-402, doi:10.1093/cid/civ295 (2015).
164 Jin, C. *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* **390**, 2472-2480, doi:10.1016/S0140-6736(17)32149-9 (2017).
165 Meiring, J. E., Giubilini, A., Savulescu, J., Pitzer, V. E. & Pollard, A. J. Generating the Evidence for Typhoid Vaccine Introduction: Considerations for Global Disease Burden Estimates and Vaccine Testing Through Human Challenge. *Clin Infect Dis* **69**, S402-s407, doi:10.1093/cid/ciz630 (2019).
166 Nampota, N. *et al.* Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months through 12 years in Malawi: results from a randomised, double-blind, controlled trial *Lancet Glob Health* (2022).
167 Sirima, S. B. *et al.* Safety and immunogenicity of co-administration of meningococcal type A and measles-rubella vaccines with typhoid conjugate vaccine in children aged 15-23 months in Burkina Faso. *Int J Infect Dis* **102**, 517-523, doi:10.1016/j.ijid.2020.10.103 (2021).
168 Patel, P. D. *et al.* Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children. *N Engl J Med* **385**, 1104-1115, doi:10.1056/NEJMoa2035916 (2021).
169 Meiring, J. E. *et al.* Typhoid Vaccine Acceleration Consortium Malawi: A phase III, randomized, double-blind, controlled trial of the clinical efficacy of typhoid conjugate vaccine among children in Blantyre, Malawi. *Clin Infect Dis* **68**, S50-s58, doi:10.1093/cid/ciy1103 (2019).
170 Colin-Jones, R. *et al.* Logistics of Implementing a Large-scale Typhoid Vaccine Trial in Kathmandu, Nepal. *Clin Infect Dis* **68**, S138-s145, doi:10.1093/cid/ciy1125 (2019).
171 Shakya, M. *et al.* Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. *N Engl J Med* **381**, 2209-2218, doi:10.1056/NEJMoa1905047 (2019).
172 Patel, P. e. a. Efficacy of typhoid conjugate vaccine: final analysis of a four-year, randomised controlled trial in Malawian children. *Preprint at SSRN: https://ssrn.com/abstract=4411421* (2023).
173 Theiss-Nyland, K. *et al.* Assessing the impact of a Vi-polysaccharide conjugate vaccine in preventing typhoid infection among Bangladeshi

children: A protocol for a phase IIIb trial. *Clin Infect Dis* **68**, S74-s82, doi:10.1093/cid/ciy1107 (2019).
174 Qadri, F. *et al.* Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial. *Lancet* **398**, 675-684, doi:10.1016/s0140-6736(21)01124-7 (2021).
175 Khanam, F. *et al.* Assessment of vaccine herd protection in a cluster-randomised trial of Vi conjugate vaccine against typhoid fever: results of further analysis. *eClinicalMedicine* **58**, doi:10.1016/j.eclinm.2023.101925 (2023).
176 Hoffman, S. A. *et al.* Programmatic Effectiveness of a Pediatric Typhoid Conjugate Vaccine Campaign in Navi Mumbai, India. *Clinical Infectious Diseases*, doi:10.1093/cid/ciad132 (2023).
177 Yousafzai, M. T. *et al.* Effectiveness of typhoid conjugate vaccine against culture-confirmed Salmonella enterica serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: a cohort study. *Lancet Glob Health* **9**, e1154-e1162, doi:10.1016/s2214-109x(21)00255-2 (2021).
178 Lightowler, M. S. *et al.* Effectiveness of typhoid conjugate vaccine in Zimbabwe used in response to an outbreak among children and young adults: A matched case control study. *Vaccine* **40**, 4199-4210, doi:10.1016/j.vaccine.2022.04.093 (2022).
179 Nampota-Nkomba, N., Carey, M. E., Jamka, L. P., Fecteau, N. & Neuzil, K. M. Using Typhoid Conjugate Vaccines to Prevent Disease, Promote Health Equity, and Counter Drug-Resistant Typhoid Fever. *Open Forum Infectious Diseases* **10**, S6-S12, doi:10.1093/ofid/ofad022 (2023).
180 Khanam, F., Ross, A. G., McMillan, N. A. J. & Qadri, F. Toward Typhoid Fever Elimination. *Int J Infect Dis* **119**, 41-43, doi:10.1016/j.ijid.2022.03.036 (2022).
181 Nga, T. V. T., Duy, P. T., Lan, N. P. H., Chau, N. V. V. & Baker, S. The Control of Typhoid Fever in Vietnam. *Am J Trop Med Hyg* **99**, 72-78, doi:10.4269/ajtmh.18-0035 (2018).
182 Browne, A. J. *et al.* Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. *BMC Med* **18**, 1, doi:10.1186/s12916-019-1443-1 (2020).
183 Bhutta, Z. A. Impact of age and drug resistance on mortality in typhoid fever. *Arch Dis Child* **75**, 214-217, doi:10.1136/adc.75.3.214 (1996).
184 Parry, C. M. The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. *Trans R Soc Trop Med Hyg* **98**, 413-422, doi:10.1016/j.trstmh.2003.10.014 (2004).
185 Nabarro, L. E. *et al.* British infection association guidelines for the diagnosis and management of enteric fever in England. *J Infect* **84**, 469-489, doi:10.1016/j.jinf.2022.01.014 (2022).
186 Dolecek C, P. S., Basnyat B, Olliaro P. . *Antibiotics for typhoid fever. In: The selection and use of essential medicines. WHO technical report series No 1021*, <https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1> (2019).
187 Carey, M. E. *et al.* Spontaneous Emergence of Azithromycin Resistance in Independent Lineages of Salmonella Typhi in Northern India. *Clin Infect Dis* **72**, e120-e127, doi:10.1093/cid/ciaa1773 (2021).

188 Duy, P. T. *et al.* The emergence of azithromycin-resistant Salmonella Typhi in Nepal. *JAC Antimicrob Resist* **2**, dlaa109, doi:10.1093/jacamr/dlaa109 (2020).
189 Effa, E. E. & Bukirwa, H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). *Cochrane Database Syst Rev*, Cd006083, doi:10.1002/14651858.CD006083.pub2 (2008).
190 Effa, E. E. *et al.* Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). *Cochrane Database Syst Rev* **2011**, Cd004530, doi:10.1002/14651858.CD004530.pub4 (2011).
191 Eliakim-Raz, N. *et al.* Efficacy and safety of chloramphenicol: joining the revival of old antibiotics? Systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* **70**, 979-996, doi:10.1093/jac/dku530 (2015).
192 Qamar, F. N. *et al.* Outbreak investigation of ceftriaxone-resistant Salmonella enterica serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. *Lancet Infect Dis* **18**, 1368-1376, doi:10.1016/s1473-3099(18)30483-3 (2018).
193 Argimón, S. *et al.* Circulation of Third-Generation Cephalosporin Resistant Salmonella Typhi in Mumbai, India. *Clin Infect Dis* **74**, 2234-2237, doi:10.1093/cid/ciab897 (2022).
194 Samajpati, S., Pragasam, A. K., Mandal, S., Balaji, V. & Dutta, S. Emergence of ceftriaxone resistant Salmonella enterica serovar Typhi in Eastern India. *Infection, Genetics and Evolution* **96**, 105093, doi:https://doi.org/10.1016/j.meegid.2021.105093 (2021).
195 Qureshi, S. *et al.* Response of extensively drug resistant Salmonella Typhi to treatment with meropenem and azithromycin, in Pakistan. *PLOS Neglected Tropical Diseases* **14**, e0008682, doi:10.1371/journal.pntd.0008682 (2020).
196 Van Be Bay, P. *et al.* Quantitative bacterial counts in the bone marrow of Vietnamese patients with typhoid fever. *Trans R Soc Trop Med Hyg* **116**, 736-744, doi:10.1093/trstmh/trac003 (2022).
197 Pascual, A., Conejo, M. C., García, I. & Perea, E. J. Factors affecting the intracellular accumulation and activity of azithromycin. *J Antimicrob Chemother* **35**, 85-93, doi:10.1093/jac/35.1.85 (1995).
198 Zmora, N. *et al.* Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults. *PLoS Negl Trop Dis* **12**, e0006380, doi:10.1371/journal.pntd.0006380 (2018).
199 Giri, A. *et al.* Azithromycin and cefixime combination versus azithromycin alone for the out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia: a randomised controlled trial protocol. *Wellcome Open Res* **6**, 207, doi:10.12688/wellcomeopenres.16801.2 (2021).
200 Butler, T. *et al.* Typhoid fever complicated by intestinal perforation: a persisting fatal disease requiring surgical management. *Rev Infect Dis* **7**, 244-256, doi:10.1093/clinids/7.2.244 (1985).
201 Hoffman, S. L. *et al.* Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. *N Engl J Med* **310**, 82-88, doi:10.1056/nejm198401123100203 (1984).
202 Contopoulos-Ioannidis, D. G. & Ioannidis, J. P. Claims for improved survival from systemic corticosteroids in diverse conditions: an umbrella review. *Eur J Clin Invest* **42**, 233-244, doi:10.1111/j.1365-2362.2011.02584.x (2012).

203 McCann, N., Scott, P., Parry, C. M. & Brown, M. Antimicrobial agents for the treatment of enteric fever chronic carriage: A systematic review. *PLoS One* **17**, e0272043, doi:10.1371/journal.pone.0272043 (2022).
204 Luthra, K. *et al.* A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines. *Clin Infect Dis* **68**, S83-s95, doi:10.1093/cid/ciy1122 (2019).
205 Riewpaiboon, A. *et al.* Cost of illness due to typhoid Fever in pemba, zanzibar, East Africa. *J Health Popul Nutr* **32**, 377-385 (2014).
206 Bahl, R. *et al.* Costs of illness due to typhoid fever in an Indian urban slum community: implications for vaccination policy. *J Health Popul Nutr* **22**, 304-310 (2004).
207 Kaljee, L. M. *et al.* Social and Economic Burden Associated With Typhoid Fever in Kathmandu and Surrounding Areas: A Qualitative Study. *J Infect Dis* **218**, S243-s249, doi:10.1093/infdis/jix122 (2018).
208 Limani, F. *et al.* Estimating the economic burden of typhoid in children and adults in Blantyre, Malawi: a costing cohort study. In progress. *BMC Public Health* (Submitted).
209 Mejia, N. *et al.* Typhoid and Paratyphoid Cost of Illness in Nepal: Patient and Health Facility Costs From the Surveillance for Enteric Fever in Asia Project II. *Clin Infect Dis* **71**, S306-s318, doi:10.1093/cid/ciaa1335 (2020).
210 Mejia, N. *et al.* Typhoid and Paratyphoid Cost of Illness in Bangladesh: Patient and Health Facility Costs From the Surveillance for Enteric Fever in Asia Project II. *Clin Infect Dis* **71**, S293-s305, doi:10.1093/cid/ciaa1334 (2020).
211 Mejia, N. *et al.* Typhoid and Paratyphoid Cost of Illness in Bangladesh: Patient and Health Facility Costs From the Surveillance for Enteric Fever in Asia Project II. *Clinical Infectious Diseases* **71**, S293-S305, doi:10.1093/cid/ciaa1334 (2020).
212 Mejia, N. *et al.* Typhoid and Paratyphoid Cost of Illness in Pakistan: Patient and Health Facility Costs From the Surveillance for Enteric Fever in Asia Project II. *Clin Infect Dis* **71**, S319-s335, doi:10.1093/cid/ciaa1336 (2020).
213 Bilcke, J. *et al.* Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *Lancet Infect Dis* **19**, 728-739, doi:10.1016/s1473-3099(18)30804-1 (2019).
214 Seyi-Olajide, J. O. *et al.* Catastrophic Healthcare Expenditure from Typhoid Perforation in Children in Nigeria. *Surg Infect (Larchmt)* **21**, 586-591, doi:10.1089/sur.2020.134 (2020).
215 Kumar, D. *et al.* Cost of Illness Due to Severe Enteric Fever in India. *J Infect Dis* **224**, S540-s547, doi:10.1093/infdis/jiab282 (2021).
216 Malik, A. (2019).
217 Limani, F. *et al.* Estimating the economic burden of typhoid in children and adults in Blantyre, Malawi: A costing cohort study. *PLOS ONE* **17**, e0277419, doi:10.1371/journal.pone.0277419 (2022).
218 Birkhold, M., Mwisongo, A., Pollard, A. J. & Neuzil, K. M. Typhoid conjugate vaccine in Africa and Asia: Status of clinical evaluation and vaccine introduction. *The Journal of Infectious Diseases*, doi:10.1093/infdis/jiab449 (2021).
219 World Health, O. in *Vaccine* Vol. 37 (2019).
220 World Health Organization. Weekly epidemiological record. 261-276 (Geneva, Switzerland, 2022).

221 Gavi the Vaccine Alliance. (2017).
222 Lo, N. C. *et al.* Comparison of Strategies and Incidence Thresholds for Vi Conjugate Vaccines Against Typhoid Fever: A Cost-effectiveness Modeling Study. *J Infect Dis* **218**, S232-s242, doi:10.1093/infdis/jix598 (2018).
223 Burrows, H. *et al.* Comparison of model predictions of typhoid conjugate vaccine public health impact and cost-effectiveness. *Vaccine* **41**, 965-975, doi:10.1016/j.vaccine.2022.12.032 (2023).
224 Chauhan, A. S. *et al.* Cost effectiveness of typhoid vaccination in India. *Vaccine* **39**, 4089-4098, doi:10.1016/j.vaccine.2021.06.003 (2021).
225 Ryckman, T. *et al.* Comparison of Strategies for Typhoid Conjugate Vaccine Introduction in India: A Cost-Effectiveness Modeling Study. *The Journal of Infectious Diseases* **224**, S612-S624, doi:10.1093/infdis/jiab150 (2021).
226 Carey, M. E., McCann, N. S. & Gibani, M. M. Typhoid fever control in the 21st century: where are we now? *Curr Opin Infect Dis* **35**, 424-430, doi:10.1097/qco.0000000000000879 (2022).
227 MacLennan, C. A., Stanaway, J., Grow, S., Vannice, K. & Steele, A. D. Salmonella Combination Vaccines: Moving Beyond Typhoid. *Open Forum Infectious Diseases* **10**, S58-S66, doi:10.1093/ofid/ofad041 (2023).
228 Shakya, M. *et al.* Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial. *Lancet Glob Health* **9**, e1561-e1568, doi:10.1016/s2214-109x(21)00346-6 (2021).
229 Batool, R. *et al.* Effectiveness of typhoid conjugate vaccine against culture-confirmed typhoid in a peri-urban setting in Karachi: A case-control study. *Vaccine* **39**, 5858-5865, doi:10.1016/j.vaccine.2021.08.051 (2021).
230 Juel, H. B. *et al.* Salmonella Typhi Bactericidal Antibodies Reduce Disease Severity but Do Not Protect against Typhoid Fever in a Controlled Human Infection Model. *Front Immunol* **8**, 1916, doi:10.3389/fimmu.2017.01916 (2017).
231 Jones, E. *et al.* A Salmonella Typhi Controlled Human Infection Study for Assessing Correlation between Bactericidal Antibodies and Protection against Infection Induced by Typhoid Vaccination. *Microorganisms* **9**, doi:10.3390/microorganisms9071394 (2021).
232 Jin, C. *et al.* Treatment responses to Azithromycin and Ciprofloxacin in uncomplicated Salmonella Typhi infection: A comparison of Clinical and Microbiological Data from a Controlled Human Infection Model. *PLoS Negl Trop Dis* **13**, e0007955, doi:10.1371/journal.pntd.0007955 (2019).
233 Jin, C. *et al.* Vi-specific serological correlates of protection for typhoid fever. *J Exp Med* **218**, doi:10.1084/jem.20201116 (2021).
234 Dahora, L. C. *et al.* IgA and IgG1 Specific to Vi Polysaccharide of Salmonella Typhi Correlate With Protection Status in a Typhoid Fever Controlled Human Infection Model. *Front Immunol* **10**, 2582, doi:10.3389/fimmu.2019.02582 (2019).
235 Cross, D. L. *et al.* Vi-Vaccinations Induce Heterogeneous Plasma Cell Responses That Associate With Protection From Typhoid Fever. *Front Immunol* **11**, 574057, doi:10.3389/fimmu.2020.574057 (2020).

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[Au: If you have consent for the patient experience Box 2 and we are able to retain the Box, I suggest to add the following statement here in the Acknowledgements: "The authors thank Bashir for their contribution in Box 2." Is this OK?]

Author contributions

[Au: I have updated this statement to match the information provided on the online tracking system. Please update here if you adjust the statement on the online system.]

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Competing interests

The authors declare no competing interests.

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