Enteric (typhoid and paratyphoid) fever

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Enteric fever, caused by the human-restricted bacteria *Salmonella enterica* serovar Typhi (typhoid) and *Salmonella enterica* serovar Paratyphi A, B, and C (paratyphoid), affects persons residing in, or travelling from, areas lacking safe water, sanitation, and hygiene infrastructure. Transmission is by the faecal–oral route. A gradual fever onset over 3–7 days with malaise, headache, and myalgia is typical. Symptoms can be altered by previous antimicrobial use. Life-threatening complications can arise in the second week of untreated illness. Differentiation from other febrile illnesses is challenging. Blood or bone marrow culture remain reference standard diagnostic methods, despite the low sensitivity of blood culture. Azithromycin, ciprofloxacin (excepting cases originating in south Asia due to drug resistance), or ceftriaxone are recommended treatment options for both typhoid and paratyphoid; however, choice should be guided by local resistance patterns. Ciprofloxacin-resistant and ceftriaxone-resistant typhoid is common in Pakistan. Three vaccine types are available for prevention of typhoid disease, including the newer, more effective typhoid Vi-conjugate vaccines. Vaccination as well as water, sanitation, and hygiene measures are cornerstones of prevention.

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Introduction

Enteric fever is an invasive infection caused by the human-restricted pathogens *Salmonella enterica* serovar Typhi (*S* Typhi; typhoid fever) and *Salmonella enterica* serovar Paratyphi A and occasionally Paratyphi B and C (*S* Paratyphi; paratyphoid fever).[1] Among populations in low-income and middle-income countries (LMICs) that lack access to safe drinking water, sanitation, and hygiene (WASH) infrastructure enteric fever is an important cause of febrile illness, causing morbidity, mortality, and an economic burden for families.[2,3] The Global Burden of Disease Study estimated 9·3 million cases of enteric fever globally in 2021.[4] The prevalence of enteric fever remains high in Asia and Africa, with an estimated 62% of the global burden in south Asia (figure 1). The global mortality in 2021 was estimated at more than 100 000 deaths each year.[4] These estimates are constrained by the limited data availability in LMICs.

Public health approaches to reduce the disease burden of enteric fever in LMICs include access to WASH and the introduction of typhoid Vi-conjugate vaccines.[5,6] Despite these steps, enteric fever remains an important cause of acute undifferentiated fever among patients in LMICs, and in returned travellers with fever from endemic areas.[2,7] Case management is challenging because the clinical presentation overlaps with other infections, diagnostic tests are unsatisfactory, and widespread antimicrobial resistance has narrowed treatment options.[8–11] This Seminar focuses on the evidence supporting effective case management of patients with suspected enteric fever.

The bacteria

S Typhi and *S* Paratyphi A, B, and C are motile Gram-negative bacteria and serovars of *Salmonella* species in the family Enterobacteriaceae. The genome of *S* Typhi contains pathogenicity islands with virulence-associated genes such as the Vi capsular antigen, flagella antigens, and type III secretion systems.[12,13] A typhoid toxin has been described, but its role in disease pathophysiology is unclear.[14,15] Humans are the sole reservoir of this infection. Genomic comparisons with non-typhoidal salmonella show areas of genome loss and inactive pseudogenes in *S* Typhi and *S* Paratyphi that are consistent with evolutionary adaption to a narrow human niche.[12,16] Genomic types vary in different global regions.[17–20] The haplotype H58 (clade 4.3.1 and derived genotypes) has been associated with the spread of antimicrobial resistance from south Asia to other regions such as east Africa.[17,20]

How do people acquire infection?

The disease is transmitted by the faecal–oral route through ingestion of food or water contaminated by human faeces or urine containing the bacterium *S* Typhi or *S* Paratyphi.[21] Transmission can occur by a short-cycle, in which faecal shedding of the bacteria in the immediate environment contaminates food and water because of

Search strategy and selection criteria

We searched MEDLINE (OVID), Embase (OVID), Global Index Medicus, and—from Web of Science—Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index–Science (CPCI-S), and Conference Proceedings Citation Index–Social Science & Humanities (CPCI-SSH), using broad terms for enteric fever (“typhoid fever”, “salmonella typhi”, “enteric fever”, “paratyphoid fever”, “salmonella paratyphi”). The search was conducted in March, 2023, with no publication date restriction, and results were restricted to English-language systematic reviews. To prioritise the most relevant and recently published studies, we also searched Medline in July, 2024, using the same search terms for all studies published in English between Jan 1, 2020, to July 1, 2024. The contacts of authors were used to identity further key studies not identified in either search until Feb 28, 2025. Reference lists of included studies were hand-searched for further relevant studies.

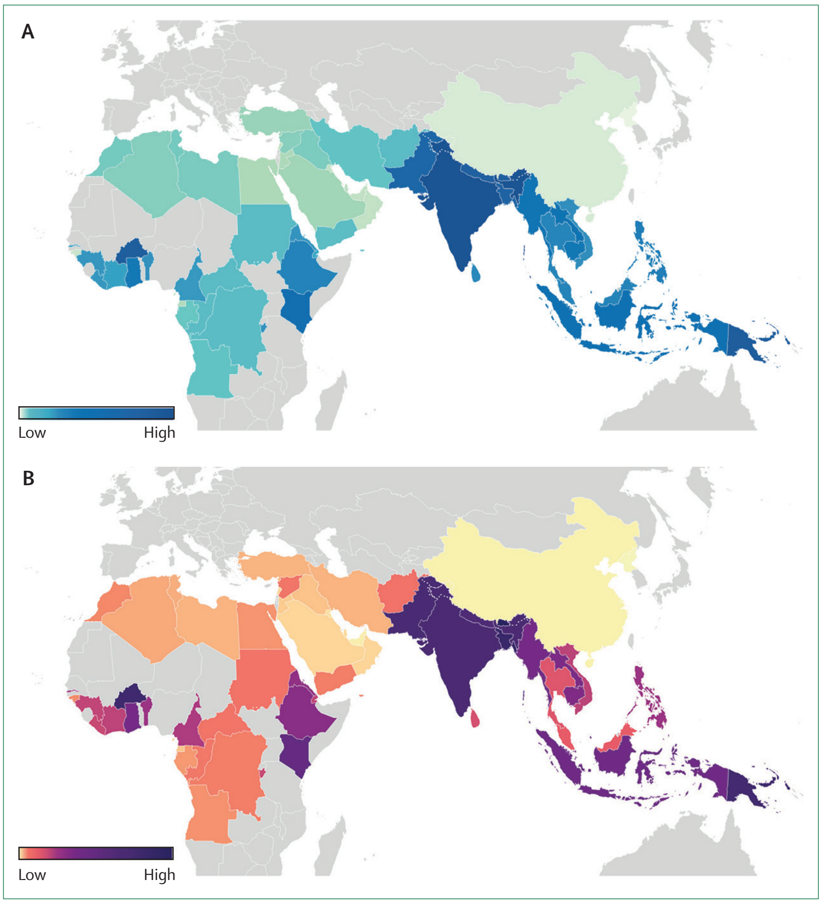

Figure 1: **Age-standardised incidence and mortality of enteric fever**
Age-standardised incidence (panel A) and mortality (panel B) of enteric fever in 75 endemic countries, per data from 2021. Reproduced from Piovani et al,[4] by permission of the authors.

inadequate hygiene and sanitation measures, or a long-cycle, in which there is contamination of the broader environment because of pollution of untreated water supplies by human faeces or when raw human faeces or untreated sewage is used as a crop fertiliser.[21]

The bacteria can survive in water and ice.[22] Contaminated fresh water, utensils, and food (including raw fruit and vegetables, food cooked at inadequate temperatures, unpasteurised dairy products, and shellfish harvested from contaminated water) can be sources of transmission.[22] Direct faecal–oral transmission and sexual transmission in men who have sex with men is reported.[23] Vertical transmission with neonatal typhoid is rare.[24]

Outbreaks of enteric fever in LMICs between 1990 and 2018 were mainly through waterborne transmission, which included faecal contamination from burst sewer pipes, lack of chlorination, unregulated water sources, and drinking water sources close to latrines.[25] In high-income countries outbreaks are more often foodborne and linked to food handlers, asymptomatic chronic carriers, or both.[26] The burden and importance of chronic carriers, defined as individuals with continued shedding of typhoidal bacteria in faeces or urine for more than a year after an acute infection (panel 1), as a source of infection in high burden areas has not been well studied.[21,27,28]

Panel 1: Terminology and definitions

Definitions of drug resistance patterns
- Multidrug resistant: resistant to chloramphenicol, amoxycillin, and trimethoprim–sulphamethoxazole
- Fluoroquinolone non-susceptible: reduced susceptibility to ciprofloxacin (minimum inhibitory concentration >0·06 mg/L); resistance to nalidixic acid or pefloxacin is a marker
- Extensively drug resistant: resistant to chloramphenicol, amoxycillin, trimethoprim–sulphamethoxazole, ciprofloxacin, and ceftriaxone

WHO case definitions
- Acute typhoid fever: laboratory confirmation by culture or molecular methods of *Salmonella enterica* serotype Typhi (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 1 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 of 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 typhoid fever
- Suspected case of typhoid: fever for at least 3 out of 7 consecutive days in an endemic area or following travel from an endemic area, or fever for a least 3 out of 7 consecutive days within 28 days of being in household contact with a confirmed case of typhoid fever

Disease pathophysiology

Human challenge studies suggest that bacteria passing through the gastric acid barrier after ingestion require an infectious dose between 10^3–10^4 bacteria for *S* Typhi and *S* Paratyphi A.[29,30] Evidence from other enteric infections suggests that reduced gastric acidity, due to gastrectomy or proton pump inhibitor treatment, could reduce the inoculum required.[31] Past infection with *Helicobacter pylori* is a further suggested risk factor.[32]

The bacteria pass through the wall of the ileum through M cells overlying the Peyers patches and are then ingested by monocyte-macrophage cells in the submucosa and mesenteric lymph nodes (figure 2).[33,34]

The bacteria survive intracellularly and travel via the lymphatic system and bloodstream to the reticuloendothelial system (liver, spleen, and bone marrow).[35] After multiplication in the reticuloendothelial system, re-invasion of the bloodstream coincides with the onset of symptoms.[33] The typical incubation period can vary according to the quantity of bacteria ingested but is typically 7–21 days, occasionally as short as 2 days, and with the majority of cases within 28 days.[36,37]

The median bacterial load in the bloodstream is only one bacteria per mL.[29,30,38,39] Children have higher blood bacterial counts than adults and the numbers for both decline with increasing duration of illness.[38] The bacterial load is ten times higher in the bone marrow.[39,40] About two-thirds of the bacteria in blood and bone marrow are intracellular.[38–40] The number of bacteria in the bone marrow correlates with the elevation in liver transaminases, and a higher proportion of bone marrow cultures are positive with increasing disease severity.[40,41] This correlation suggests that bacteria in the reticuloendothelial system reflect the in-host bacterial disease burden. Cytokines, such as TNF and IL-6, have been shown to be moderately elevated in blood but less so than seen in Gram-negative septic shock.[34] Specific host genetic polymorphisms, such as variation at *HLA-DRB1*, have been associated with risk of typhoid and severe disease.[42]

As the bacteria pass through the biliary system, gall bladder, and then back into the small intestine, in some patients the bacteria incite an inflammatory reaction at the sites of initial systemic entry in the terminal ileum. Ulceration, bleeding, and necrosis of the Peyer's patches can occur in Shwartzman and Koch type reactions.[43] This reaction can lead to gastrointestinal bleeding as well as intestinal perforation and peritonitis (figure 3A).

Short-term shedding of bacteria in the faeces can occur before and during acute infection and in the few weeks following clinical recovery.[21,29,30,44–46] Chronic carriage predominantly occurs in the context of gall bladder disease (panel 1, figure 3B) and rarely at other sites in the biliary system and urinary tract.[21,47–49] The bacteria form a dense bacterial biofilm on gallstones and other surfaces, occasionally also involving the intrahepatic bile ducts.[50] Chronic faecal carriage occurs in 2–5% of people after acute typhoid fever, is more common in females than males, and increases with age.[44] A quarter of asymptomatic carriers have no history of acute typhoid fever, and shedding in the faeces is sporadic.[44]

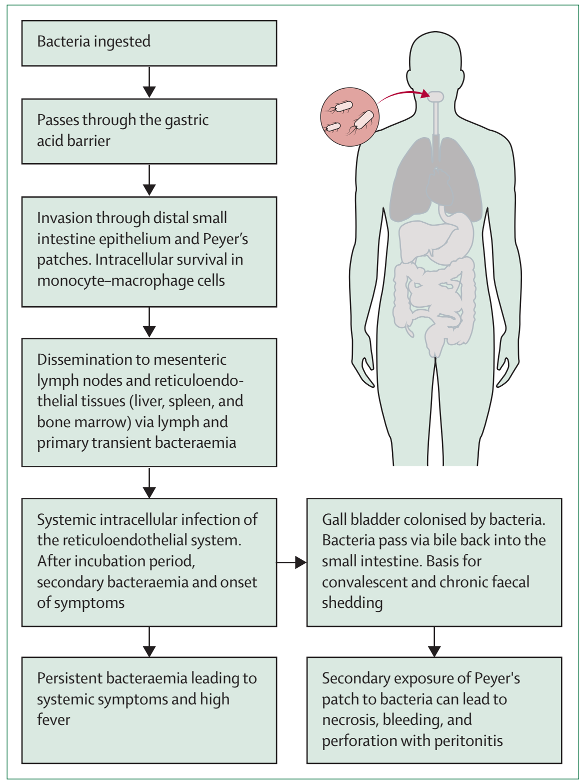

Figure 2: **Stages in the pathophysiology of enteric fever**

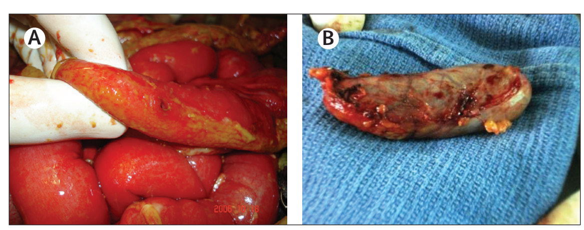

Figure 3: **Typhoid-related intestinal perforation and diseased gall bladder**
(A) A single perforation in the terminal ileum of a child in Viet Nam seen at laparotomy due to typhoid fever infection. (B) Diseased gall bladder removed from a Nepalese patient with chronic faecal carriage; *Salmonella enterica* serovar Typhi was isolated from the gall bladder contents.

Where in the world should enteric fever be considered as a differential diagnosis?

Most populations living in ecological conditions conducive to enteric fever transmission do not have population-based national surveillance systems and have poor access to diagnostic blood-culture facilities. In addition, there have been few high-quality primary incidence studies, as highlighted in a systematic review and meta-analysis of global typhoid fever incidence studies published between 1946 and 2018.[51] The review described high levels of disease in south and southeast Asia and some parts of sub-Saharan Africa. Since this review, further robust estimates have been derived from research studies conducted in affected regions using methodology that establish incidence by combining active blood culture surveillance with health utilisation surveys and adjustments for blood culture sensitivity.[52–56] Incidence rates exceeding 100 per 100 000 person-years is a threshold used to define settings as high burden for enteric fever.[21]

Prospective population-based studies between 2016 and 2019 reported the adjusted incidence of typhoid fever per 100 000 person-years: Garrett and colleagues[52] reported 913 in Dhaka, Bangladesh, 330 in Kathmandu, Nepal, and 103 in Karachi, Pakistan; and Meiring and colleagues[53] reported 1135 in Dhaka, Bangladesh, 1062 in Kathmandu, Nepal, and 176 in Karachi, Pakistan. The adjusted incidence rates for paratyphoid per 100 000 person-years were 128 and 42 in Bangladesh, 46 and 6 in Nepal, and 23 and 1 in Pakistan. The highest incidence of disease was in children aged 2–4 years in Bangladesh and Pakistan but cases in children younger than 2 years were also reported. In Nepal, the highest incidence was among individuals aged 5–25 years. A prospective study conducted in children at three urban sites and one rural site in India between 2017 and 2020 gave estimated typhoid fever incidences ranging from 12 to 1622 per 100 000 child-years between the ages of 6 months and 14 years and from 108 to 970 per 100 000 person-years in those aged 15 years or older.[54] The overall incidence of paratyphoid was 68 per 100 000 child-years.

Surveillance studies conducted in 12 African countries have shown a wider variation of typhoid fever incidence compared with south Asia.[53,55–57] Incidences above 100 per 100 000 person-year observations have been documented in sites in Burkina Faso, Ghana, Madagascar, Tanzania, Kenya, Democratic Republic of Congo, Nigeria, and Malawi, with lower levels in other countries.[53,55–57]

General features
- Fever
- Malaise
- Myalgia
- Arthralgia
- Poor appetite

Respiratory
- Dry cough
- Wheeze
- Bronchitis
- Pneumonia

Gastrointestinal
- Abdominal pain
- Abdominal distension
- Nausea
- Vomiting
- Anorexia
- Constipation
- Diarrhoea
- Intestinal perforation
- Gastrointestinal bleeding

Liver, spleen, and gall bladder
- Hepatosplenomegaly
- Hepatitis
- Jaundice
- Cholecystitis
- Chronic faecal carriage

CNS
- Headache
- Mental dullness
- Delirium
- Encephalopathy
- Febrile seizures
- Meningitis
- Psychosis
- Movement disorders

Cardiovascular
- Asymptomatic ECG changes
- Relative bradycardia
- Myocarditis
- Haemodynamic shock
- Endocarditis

Renal
- Cystitis
- Nephritis
- Acute kidney injury

Haematological
- Anaemia
- Thrombocytopenia
- Disseminated intravascular coagulation

Other
- Rose spots
- Septic arthritis
- Osteomyelitis
- Focal abscess (eg, parotitis, brain, spleen, and kidney)

Figure 4: **Signs, symptoms, and complications in enteric fever**
Common signs and symptoms in black, complications in red. ECG=electrocardiogram.

Similar data on incidence rates from other regions in the world are generally lacking. Some countries within Oceania have reported high incidence levels.[4,58] Data from Latin America are also sparse, but suggest the incidence is low.[4,28]

Overall, these studies have shown an appreciable burden of enteric fever in children younger than 15 years, with high levels in urban and some rural areas. The burden of enteric fever is dynamic as WASH interventions and vaccination can lead to reductions in transmission while evolving patterns of increasing antimicrobial resistance can increase incidence in different settings over time.[10,20] Incidence patterns will continue to evolve with the potential effects of climate change, population growth, extreme weather events, and urbanisation.[59]

How does enteric fever present?

In the classic descriptions of enteric fever, the illness begins with a gradual onset of fever over 3–7 consecutive days, a step ladder of increasingly high temperature spikes, with general malaise, headache, a dry cough, and myalgia (figure 4).[60–62] Occasionally the disease presents with a more acute onset but without the paroxysms and chills seen in malaria. Untreated enteric fever progresses in the second week of illness with a high persistent fever, sometimes with a relative bradycardia, a palpable liver or spleen and with increasing mental dullness and confusion. If left untreated, in the second and third week complications develop.[60–62] This classic progression is more rarely seen now as patients generally present early to medical care, after a few days of fever, and have frequently already taken antimicrobial therapy from a shop or pharmacy before attending a health-care provider.

In recent descriptions in children, common clinical features are consecutive days of high-grade fever (39–40°C), nausea, vomiting, diarrhoea, constipation, hepatomegaly, splenomegaly, and abdominal distension.[63,64] Anaemia and leukopenia are common laboratory findings. Young, pre-school age children can present with a non-specific fever without localising signs and inconclusive laboratory results, or alternatively with toxicity and atypical clinical features.[63,64]

In adults, gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea, or constipation) with over three consecutive days of slowly rising fever raise the suspicion of enteric fever.[63,65] Headache, anorexia, hepatosplenomegaly, and cough can occur. Rose spots are blanching, erythematous, maculopapular lesions, 2–4 mm in diameter that usually occur on the trunk; when present they are transient, difficult to see on darker skin tones, and in recent reviews reported in less than 10% of cases.[63] They are not pathognomonic for enteric fever. Occasionally, young children and adults can have a short febrile illness with a transient bacteraemia with none of the typical features of typhoid fever.[21,29,30,66] Paratyphoid fever has been found to be clinically indistinguishable from typhoid in some studies but described as a milder disease in others.[65,67] A patient story is described in panel 2.

Possible complications

Complications generally develop in untreated disease in the second or third week of illness following late presentation to medical care or the delayed initiation of appropriate antimicrobial treatment (figure 4).[62,68] Multidrug-resistant (MDR; ie, resistant to ampicillin, chloramphenicol, and co-trimoxazole),[69] fluoroquinolone non-susceptible (FQNS),[70] and extensively drug resistant (XDR; ie, MDR, FQNS, and ceftriaxone-resistant)[71] infections have been implicated as risk factors for complications (panel 1). A high bacterial inoculum could also be a risk factor for complications.[38] There is no strong evidence to suggest an association between HIV and enteric fever occurrence and/or severity, unlike with the non-typhoidal *Salmonella*.[72] Recent case–fatality ratio (CFR) estimates are in the range of 0·3–6·7% overall,[70,73–75] 4·45% in hospitalised cases,[74] and up to 15·5% in cases with typhoid intestinal perforation.[73]

Typhoid intestinal perforation is a life-threatening complication (figure 3A). In studies in Africa, one in five patients with typhoid intestinal perforation died.[76] Lack of prompt access to surgical resources, intensive care, and postoperative care could contribute to these deaths.[76–79] Common postoperative complications include surgical site infection, wound dehiscence, and enterocutaneous fistula, all of which increase length of hospital stay and place substantial economic burden on families.[78–80]

The syndrome of encephalopathy is also associated with high mortality.[81–83] An abnormal affect with mental dullness can occur.[11,61–65] In some patients, mental dullness can progress to delirium, abnormal movements, obtundation, and coma accompanied by toxicity, evidence of myocarditis, and haemodynamic shock.[81–83] The pathogenesis of the syndrome is not well established.

Many other complications occur in enteric fever (figure 4). Gastrointestinal bleeding is relatively common, but is rarely life threatening. Hepatitis, cholecystitis, acalculous cholecystitis, pneumonia, and anaemia are also common complications in some case series.[60–64,68–71] Rare complications include septic arthritis and osteomyelitis, extra-intestinal abscesses, meningitis and brain abscess in the very young, splenic infarcts and rupture, spontaneous primary pneumothorax, catatonia, psychosis, and sensorineural hearing loss.[60–64,68–71] Recurrence of the illness with the same symptoms and signs can occur within 2–4 weeks of apparent recovery. This recurrence is usually a relapse of the original infection, but occasionally can be a re-infection, and this can be distinguished by molecular typing.[84]

What diagnostic tests are available?

Making a confident diagnosis of enteric fever based on clinical features alone is challenging. Non-specific signs and symptoms overlap with those of other common febrile illnesses. Malaria is an important differential but can be excluded with a blood smear or malaria rapid diagnostic test (RDT). Other important differential diagnoses include flavivirus illness (eg, dengue, chikungunya, or Zika), rickettsia infections (eg, scrub and murine typhus), leptospirosis, brucella, and other acute viral infections (eg, influenza, acute hepatotropic viruses).[11,65] RDTs are available to help with the diagnosis of some of these infections in resource-poor settings.[85] Attempts to develop a clinical diagnostic score for enteric fever have not been successful.[65]

Simple laboratory tests could help. The total white cell count is usually within, or just below, the normal range in enteric fever.[60–65] Leucocytosis (raised white cell count) could point toward intestinal perforation or an occult pyogenic infection, or leptospirosis or scrub typhus. A mild normochromic or hypochromic anaemia, mild thrombocytopenia, and mild elevation of liver transaminases with a normal bilirubin are common. C-reactive protein is also usually elevated.

Blood culture is the pragmatic reference standard test, but has a sensitivity that varies in different reports from 40% to 80% and might not be available where enteric fever is common.[86,87] In a systematic review of studies comparing blood culture with bone marrow culture, sensitivity of blood culture was 66% when

Panel 2: Clinical case

A male health-care worker in India, aged 34 years and previously well, presented to a hospital in south India with 5 days of fever up to 39°C, rigors, myalgia, and anorexia. There was no history of abdominal pain, nausea, vomiting, diarrhoea, cough, dyspnoea, altered sensorium, seizure, or focal neurological deficits. He had no recent travel and had not consumed street food. His temperature on admission was 37·7°C, pulse 110 beats per minute, blood pressure 110/80 mm Hg, respiratory rate 20 breaths per minute, and Glasgow Coma Scale score of 15. Systems examination was normal, with the exception of a coated tongue. The patient was admitted, started on empirical treatment with 1 g of azithromycin once daily and intravenous paracetamol. His laboratory testing reported C-reactive protein of 92·5 mg/L (normal range <5 mg/L) and normal complete blood count, liver transaminases, urea, and creatinine. Rapid diagnostic tests for scrub typhus, malaria, microfilariae, and dengue were negative. A chest x-ray and abdominal pelvic ultrasound were normal. His blood culture was positive after 14 h with a Gram-negative bacillus seen on microscopy; the isolate was subsequently confirmed to be *Salmonella enterica* serovar Typhi, susceptible to azithromycin and ceftriaxone and resistant to ciprofloxacin. The patient continued with azithromycin and remained febrile until day 4 of admission. Azithromycin was continued for a total of 7 days, at which point the patient was discharged having made a full recovery.

compared with bone marrow culture results.[86] The low numbers of *S* Typhi present in blood and the frequency of previous antimicrobial treatment are key reasons for the low sensitivity of blood culture;[38,87] a large volume of blood in the blood culture should increase the culture yield.[88] The estimated sensitivity of bone marrow aspirate is greater than 90%, and it can remain positive for several days even after starting effective antimicrobials.[39,40,86,89] This high yield of bone marrow aspirate culture reflects the higher bacterial load in the reticuloendothelial system than in blood.[39] Although bone marrow aspiration is technically challenging and more invasive than a blood culture, it can be valuable as a second-line investigation in patients with prolonged fever and a negative blood culture to help distinguish from differentials such as brucellosis or tuberculosis. The presence of typhoidal *Salmonella* in stool or urine could indicate acute enteric fever, but could also represent chronic carriage with a different reason for the fever.[88]

The detection of specific DNA sequences of the *S* Typhi or *S* Paratyphi genome in clinical samples is a further diagnostic option.[35,90,91] The relatively low amount of bacterial DNA found in human blood makes detection challenging. The expense and technical challenges of molecular diagnostics in laboratories in an endemic setting are an additional barrier.

The Widal test is still widely used in LMICs because it is cheap and simple to perform, although it lacks standardisation of reagents and validated cut-offs for diagnosis of an acute enteric fever.[88] The Widal test detects agglutinating antibodies against *S* Typhi and *S* Paratyphi lipopolysaccharide (O) antigens and flagellar (H) antigens.[88] False-positive results, due to past infection or cross-reacting antibodies with other Enterobacteriaceae, or false-negative results due to low levels of antibody, are common.[61] Paired acute and convalescent serum samples can show a rising antibody titre or seroconversion, but in practice decisions are made on the basis of a single acute sample, which can often be misleading. The lack of diagnostic accuracy means the Widal test cannot be recommended as a reliable diagnostic option.

Commercially available RDTs are also widely used, although many have not undergone formal diagnostic accuracy evaluation. Of those that have been evaluated, such as Typhidot-M (Reszon Diagnostics International, Malaysia), TUBEX-TF (IDL Diagnostics, Sweden), Test-it Typhoid IgM (Life Assay Diagnostics, South Africa), and Enterocheck WB (Tulip Diagnostics, India), although an improvement over the Widal test, the diagnostic accuracy is not sufficient for these tests to be recommended.[92–94] However, in reality, in many LMICs a Widal test or an RDT are the only diagnostic tests available.

Other diagnostic tests are in development. The typhoid/paratyphoid diagnostic assay detects *S* Typhi and *S* Paratyphi A IgA antibody secreted by isolated T cells, and performed well in studies conducted in south Asia.[94] Encouraging data on IgA serology responses against the HylE antigens have been found in studies in Nigeria and Bangladesh.[95–97] Other research approaches include studying host gene signatures[98] and diagnostic plasma metabolites.[99] Vi serology has been used to identify chronic faecal carriers in outbreak settings but performs poorly in endemic areas.[100,101] New immunogenic antigens and metabolite biomarkers for the detection of chronic carriage are being explored.[102,103]

	First-line treatment	Alternative treatment
Uncomplicated enteric fever		
Unknown susceptibility	Azithromycin, 20 mg/kg per day, 7–10 days	..
Fully susceptible	Ciprofloxacin, 20 mg/kg per day, 7–10 days	Chloramphenicol*, 50–75 mg/kg per day, 14–21 days; amoxicillin, 75–100 mg/kg per day, 14–21 days; trimethoprim–sulphamethoxazole†, 8–40 mg/kg per day‡, 14–21 days; cefixime, 20 mg/kg per day, 7–14 days; ofloxacin 10–15 mg/kg per day, 7–10 days; levofloxacin 10–15 mg/kg per day, 7–10 days
Multidrug resistant§	Ciprofloxacin, 20 mg/kg per day, 7–10 days	Cefixime, 20 mg/kg per day, 7–14 days; azithromycin, 20 mg/kg per day, 7–10 days; ofloxacin 10–15 mg/kg per day, 7–10 days; levofloxacin 10–15 mg/kg per day, 7–10 days
Fluoroquinolone non-susceptible¶	Azithromycin, 20 mg/kg per day, 7–10 days	..
Extensively drug resistant‖	Azithromycin, 20 mg/kg per day, 7–10 days	..
Severe enteric fever requiring parenteral treatment**††		
Unknown susceptibility	Ceftriaxone, 50–75 mg/kg per day, 10–14 days	..
Fully susceptible	Ciprofloxacin‡‡, 20 mg/kg per day, 10–14 days	Ceftriaxone, 50–75 mg/kg per day, 10–14 days
Multidrug resistant§	Ciprofloxacin‡‡, 20 mg/kg per day, 10–14 days	Ceftriaxone, 50–75 mg/kg per day, 10–14 days
Fluoroquinolone non-susceptible¶	Ceftriaxone, 50–75 mg/kg per day, 10–14 days	Azithromycin§§, 20 mg/kg per day, 10–14 days
Extensively drug resistant‖	Meropenem, 60 mg/kg per day, 10–14 days	Azithromycin§§, 20 mg/kg per day, 10–14 days

Culture and susceptibility result often unavailable; empirical treatment should be based on regional knowledge of susceptibility patterns.[11,104,105,107–109] *Can cause bone marrow suppression, oral route preferred. †Inexpensive, can cause allergic reactions and nephrotoxicity, not suitable during pregnancy or for children younger than 2 years. ‡8 mg/kg trimethoprim and 40 mg/kg sulphamethoxazole. §Resistant to chloramphenicol, amoxycillin, trimethoprim–sulphamethoxazole. ¶Non-susceptible to ciprofloxacin (nalidixic acid or pefloxacin resistant or ciprofloxacin resistant by disk testing). ‖Resistant to chloramphenicol, amoxycillin, trimethoprim-sulphamethoxazole, ciprofloxacin, and ceftriaxone. **In intestinal perforation, antimicrobial therapy should cover other aerobic and anaerobic gastrointestinal bacteria. ††In severe typhoid (characterised by delirium, obtundation, coma, or shock) dexamethasone can be beneficial; one 3 mg/kg dose dexamethasone infused intravenously over 30 min, followed by eight doses of 1 mg/kg every 6 h. ‡‡Ofloxacin and levofloxacin are effective alternatives. §§Consider combining meropenem with azithromycin.

Table 1: **Antimicrobial treatment options for enteric (typhoid and paratyphoid) fever**

Treatment

Patients with enteric fever require treatment with an antimicrobial agent, supportive care, and the management of complications.[11,61,62,104,105] In LMIC settings, patients are usually treated empirically in the first week of illness with an oral antimicrobial as part of outpatient management, and most recover within a week.[61] Hospital admission is required for patients with persistent vomiting who are unable to tolerate fluids and oral medications, with signs of severe dehydration or unstable vital signs and clinician concern of toxicity. Further indications for hospital admission include features of severe or complicated disease, signs of severe disease as per the Integrated Management of Childhood Illness, or where the diagnosis is uncertain.[11] Patients might decline hospital admission due to various factors, including treatment costs. Returning travellers are usually admitted to hospital until stable, although outpatient management can be a suitable alternative in the absence of complications.[106]

Antimicrobials used for treating enteric fever have included chloramphenicol, amoxicillin, trimethoprim–sulphamethoxazole, fluoroquinolones (eg, ciprofloxacin, ofloxacin, and levofloxacin), azithromycin, and cephalosporins (eg, ceftriaxone and cefixime). Systematic reviews of the comparative efficacy of antimicrobials in enteric fever treatment have been unable to draw firm conclusions on the presence or absence of important differences when the infecting isolate is susceptible to that agent. In addition, many of the individual randomised controlled trials have methodological weaknesses.[107–109]

The choice of antimicrobial depends on local or national guidelines, ideally informed by epidemiological data of local antimicrobial resistance patterns (table 1).[11,104,105,110–116] Common resistance patterns vary by location and over time.[10,20] WHO guidelines recommend that ciprofloxacin, ceftriaxone, and azithromycin should be considered first-choice treatments.[104] Treatment durations of 7–14 days or >5 days after fever resolution have traditionally been recommended. Shorter courses of treatment might be effective in uncomplicated disease and could be useful in outbreak situations in LMICs.[107,109]

Ciprofloxacin is not a suitable choice in much of south Asia and some areas of sub-Saharan Africa because of widespread low-level resistance (indicated by resistance to nalidixic acid or pefloxacin) and localised high-level resistance.[10,20,115] Azithromycin is currently an effective option. There are scattered reports of in-vitro azithromycin resistance based on a minimum inhibitory concentration breakpoint for susceptibility of ≤16 mg/L.[116–118] Of note, the clinical response to azithromycin when the in-vitro minimum inhibitory concentrations of the infecting isolate is >16 mg/L is yet to be fully defined. For children, patients admitted to hospital, and when resistance to other drugs is uncertain, parenteral ceftriaxone has been a safe option. Since 2017 there has been a large and ongoing outbreak of XDR typhoid in Pakistan.[119,120] For XDR typhoid, meropenem can be used in severe illness and azithromycin can be used in the outpatient setting.[114,121] The cephalosporin resistance in XDR strains is mediated by carriage of a plasmid-mediated $bla_{CTX\text{-}M\text{-}15}$ extended spectrum β-lactamase gene.[120] These infections have also been seen in other countries in travellers from Pakistan.[114] There are sporadic reports of other patterns of extended-spectrum cephalosporin resistance and carbapenem resistance in India and elsewhere.[122–125] Although paratyphoid fever has remained susceptible to most antimicrobials except ciprofloxacin, at the point of presentation paratyphoid cannot be differentiated from typhoid.[67,126]

Antimicrobial adjustments are warranted if antimicrobial resistance from organisms isolated in culture is reported or if clinical symptoms do not improve after 5 days of appropriate antimicrobial therapy. Typical defervescence time ranges from 5 days to 7 days when patients are on an effective antimicrobial, and patients often feel better before their temperature returns to normal.[11,61,62] Persistent fever in the absence of other signs of complications with otherwise general clinical improvement is not a marker of treatment failure. De-escalation of intravenous to oral antimicrobials should be considered on the basis of susceptibility results. If a blood culture shows no growth or is unavailable, and clinical suspicion is strong, a therapeutic trial with an appropriate antimicrobial based on local resistance patterns is appropriate. In areas where infections such as scrub or murine typhus and leptospirosis are common and can mimic enteric fever, the addition of empirical doxycycline should be considered.

Whether there is added benefit of using combinations of antimicrobials in enteric fever, compared with the efficacy of each drug on its own, is unclear. Combining the high intracellular concentrations of azithromycin with the extracellular activity of a β-lactam antimicrobial has been suggested to be useful in small, uncontrolled clinical trials.[127] An ongoing clinical trial is examining the efficacy of an azithromycin and cefixime combination in suspected cases of enteric fever in south Asia.[128] Other antimicrobials could be needed if resistance to all current options emerges.[129]

Management of complications

Patients who develop complications require additional supportive treatments, including full intensive care support, blood transfusion for a gastrointestinal haemorrhage, and surgery if there is an intestinal perforation and peritonitis.[78,79,130] Antimicrobial choice could need to be broadened in the event of a perforation causing a peritonitis; however, other complications generally resolve with effective antimicrobial therapy. Relapse rates vary between 2% and 10% but depend on the antimicrobial treatment given and the resistance pattern of the infecting organism.[107–109] Relapse usually responds to a further course of the same antimicrobial used for the primary episode.[11,61,62]

In severe typhoid characterised by altered consciousness and haemodynamic shock, a randomised controlled trial (RCT) in Indonesia found that high doses of dexamethasone (3 mg/kg followed by 1 mg/kg every 6 h for a total of 48 h) reduced mortality in patients treated

	Mechanism and type	Dose and route	Eligible persons	Protective efficacy*
Ty21a	Live attenuated, Ty2 strain of S Typhi	3 or 4 oral doses on alternate days†	Age ≥6 years; immunocompetent non-pregnant	43% (30–55) at 1–5 years‡
Vi-PS	Purified Vi capsular polysaccharide of Ty2 S Typhi strain	Single injection	Age ≥2 years	58% (44–69) at 1–3 years‡
TCV (Vi-TT)	Subunit, Vi capsular polysaccharide linked to tetanus toxoid	Single injection	Age 6 months to 65 years	83% (77–88) at 1–2 years§; 78% (66–86) at 4 years¶; 54% (13–76) at 3–5 years‖
TCV (Vi-DT)	Subunit Vi capsular polysaccharide linked to diphtheria toxoid	Single injection	Age 6 months to 45 years	Pre-approval based on immunogenicity data**
TCV (Vi-CRM_{197})	Subunit Vi capsular polysaccharide linked to CRM_{197}	Single injection	Age 6 months to 45 years	Pre-approval based on immunogenicity data**

S Typhi=*Salmonella enterica* serotype Typhi. *Data are percentage (95% CI). †Canada and the USA recommend a 4-capsule course. ‡Systematic review and meta-analysis, calculated as: (1 – risk ratio) × 100%.[5] §Randomised controlled trials and adjusted cluster randomised controlled trial, calculated as: (1 – incidence rate ratio) ×100%.[5] ¶Randomised controlled trial in children in Malawi.[139] ‖Extrapolated medium-term efficacy from a cluster randomised controlled trial in Bangladesh.[140] **WHO prequalified vaccines.[135]

Table 2: **Current prequalified vaccines for typhoid fever**

with chloramphenicol.[81] Methodological issues make it difficult to draw definitive conclusions from this study and further trials on the utility of steroids in encephalopathy and shock are needed.[131]

Chronic faecal carriers can be a source of infection to others in the community. A systematic review of studies of the antimicrobial treatment of chronic carriage identified eight studies but only one RCT.[132] Fluoroquinolones are effective in eradicating chronic carriage of susceptible isolates after a 28-day course. Results of the only double-blind RCT 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 amoxycillin in a 4–6-week course with cure rates around 70%. Cholecystectomy could be an option but should be balanced with the risk of surgical complications (figure 2B). These studies pre-date the emergence of widespread drug resistance and further clinical trials in this area, for example using azithromycin, would help guide modern management.

Prevention of enteric fever

Enteric fever can be prevented through wider access to safe drinking water, improved WASH infrastructure, education on food hygiene practices, public health disease surveillance systems (including identification, treatment, and contract tracing of chronic carriers), and vaccination.[6,26,133,134] Safe water sources and point-of-use interventions for untreated water (including chlorination or solar disinfection) have been proven to be highly effective in preventing transmission of faecal–oral pathogens.[135] WASH interventions carry the potential to have the greatest impact in regions of high disease burden.

WHO has approved a live oral attenuated vaccine (Ty21a), a Vi polysaccharide and, more recently, has prequalified three types of typhoid conjugate vaccine (TCVs) for the prevention of typhoid fever (table 2).[136,137] Other TCVs have been licensed by national regulatory authorities. The level of protection with TCVs has been shown to be high compared with the previous approved vaccines, and in 2018 WHO recommended the use of single-dose TCV in high-burden typhoid areas and areas with high rates of antimicrobial resistance.[133]

The Ty21a vaccine is approved for individuals aged 6 years and older and is an oral capsule. In a recent systematic review and meta-analysis, the random effects pooled efficacy was 43% (95% CI 30–53) at 1–5 years post-vaccination.[5] Recommendations for a three dose or four dose schedule vary between countries and comparative efficacy of these varying dosing schedules is lacking. Rare side-effects include fever, nausea, or vomiting.[136] Ty21a vaccines might not be reliably accessible in endemic regions, including Bangladesh, India, and Pakistan. Purified capsular-polysaccharide-based vaccines are available as a single intramuscular injection for individuals aged 2 years and older, providing up to 3 years of protection. The random effects pooled efficacy 1–3 years post vaccination was 58% (44–69).[5] Side-effects are rare but include fever or local reactions at the injection site.[136] Although these older vaccines are widely used for preventing typhoid in travellers to endemic areas, they have not found a place in public health programmes in high burden settings.

TCVs have been developed to provide better and durable immune protection against typhoid in endemic settings.[133] TCVs are based on Vi-polysaccharide conjugated to carrier proteins such as tetanus toxoid (Vi-TT), CRM_{197}, diphtheria toxoid, or recombinant *Pseudomonas aeruginosa* exotoxin A. A systematic review estimated the pooled efficacy of a single dose of TCV (Vi-TT) to be 83% (95% CI 77–88) at 1–2 years post-immunisation based on data from studies conducted in Bangladesh, India, Malawi, and Nepal including more than 100 000 participants aged 6 months to 16 years.[5,138–140] The effectiveness of TCV was lower in children aged 5 years and younger (73% [53–85]) compared with children older than 5 years (87% [80–91]).[5] Follow-up data showed high protection after 4 years in a cohort from Malawi (78% [66–86]).[141] A decline in vaccine effectiveness was observed after 3–5 years, dropping as low as 54% (13–76) in a cohort in Bangladesh.[142] Given that antibody titres were lower in children aged younger than 2 years, a booster vaccination could be beneficial in this age group, but this question is yet to be resolved.[143] Side-effects such as fever, local swelling, and seizures occurred rarely with TCVs in children and adults. Children younger than 5 years were mainly affected by febrile seizures, as they are in the general population. No long-term sequelae have been reported.[144]

To date, WHO lists three types of TCV as prequalified vaccines and recommends the use of single-dose TCV in high-burden typhoid areas and areas with high rates of antimicrobial resistance.[133,137] Several countries, including Bangladesh, Burkina Faso, India, Kenya, Liberia, Malawi, Nepal, Pakistan, Samoa, and Zimbabwe, have introduced TCV in routine vaccination programmes and additional mass vaccination campaigns were conducted in Tuvalu and Fiji.[6,145] The introduction of TCVs in the routine immunisation programmes in LMICs is a crucial step toward the control of this important disease.[6] Although these vaccines are not yet universally licensed, their demonstrated advantages over earlier vaccines suggest that recommendations for travellers to endemic areas are likely to be updated in the future.

The absence of licensed vaccines to prevent paratyphoid fever is a gap, although studies of potential vaccines are in progress.[146] Challenges in disease surveillance, diagnostics, and vaccine efficacy in endemic areas reinforce the need to implement WASH interventions.

Conclusions

Case management of enteric fever remains challenging. Current diagnostic tests for acute enteric fever do not have the diagnostic accuracy to be reliably used at the point of care, resulting in overuse of antimicrobials and empiric treatment.[8] A cheap, reliable, and accurate enteric fever diagnostic would provide a step change in treatment and disease control.[147] There is a looming threat of further antimicrobial resistance, and steps to prepare with data on the efficacy of alternative antimicrobials for treatment are needed.[9,10,129] Effective antimicrobial treatments are needed that cure symptoms but also stop shedding of bacteria in faeces that drives onward transmission.[21] Considering the high level of adaptation of these bacteria to a narrow niche, with humans the only natural host and reservoir,[33] the deployment of typhoid conjugate vaccines, strengthening of WASH infrastructure, development of accurate point of care diagnostics, provision of effective antimicrobial regimens, and novel approaches to the detection and treatment of chronic carriers, could make the elimination of enteric fever an achievable goal.[148]

Contributors

RK and CMP performed all literature searches. All authors contributed to drafting the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Declaration of interests

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Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and text.

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