Typhoid and paratyphoid fever

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Typhoid fever is estimated to have caused 21·6 million illnesses and 216 500 deaths globally in 2000, affecting all ages. There is also one case of paratyphoid fever for every four of typhoid. The global emergence of multidrug-resistant strains and of strains with reduced susceptibility to fluoroquinolones is of great concern. We discuss the occurrence of poor clinical response to fluoroquinolones despite disc sensitivity. Developments are being made in our understanding of the molecular pathogenesis, and genomic and proteomic studies reveal the possibility of new targets for diagnosis and treatment. Further, we review guidelines for use of diagnostic tests and for selection of antimicrobials in varying clinical situations. The importance of safe water, sanitation, and immunisation in the presence of increasing antibiotic resistance is paramount. Routine immunisation of school-age children with Vi or Ty21a vaccine is recommended for countries endemic for typhoid. Vi vaccine should be used for 2–5 year-old children in highly endemic settings.

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Typhoid fever is a systemic infection caused by *Salmonella enterica* serotype typhi (*S typhi*). A very similar but often less severe disease is caused by *S paratyphi* A, B, and sometimes C. *S typhi,* a highly adapted human-specific pathogen that evolved about 50 000 years ago,[1] has remarkable mechanisms for persistence in its host.[2]

The incidence of typhoid fever has declined greatly with the provision of clean water and good sewage systems in Europe and the USA since the early 20th century,[3] but the disease remains a serious public-health problem in developing countries.[4] The advent of chloramphenicol treatment changed the perception of typhoid fever from a severe, often fatal, disease to a common, readily manageable infection.[5] Outbreaks of chloramphenicol-resistant typhoid were reported in 1972.[6] At this time, the isolates were still sensitive to co-trimoxazole and ampicillin or amoxycillin. In the late 1980s and 1990s, outbreaks of typhoid caused by organisms resistant to chloramphenicol, co-trimoxazole, ampicillin, and amoxycillin were reported.[6] Currently, fluoroquinolones and third-generation cephalosporins are the drugs of choice for treatment of typhoid fever, but decreased susceptibility to these antimicrobials has been reported.[7–10] There is an urgent need to keep the possible emergence of untreatable strains to a minimum, by prudent use of existing drugs and by resisting the temptation to use yet more antimicrobials.

Disease burden

Typhoid is estimated to have caused 21·6 million illnesses and 216 500 deaths globally in 2000.[4] The incidence of typhoid was high (>100 cases per 100 000 population per year) in south-central Asia, southeast Asia, and possibly southern Africa, medium (10–100 cases per 100 000) in the rest of Asia, Africa, Latin America, and Oceania, except for Australia and New Zealand, and low in the other parts of the world (<10 cases per 100 000). These estimates are based on blood-culture-positive cases in 22 population-based studies, many of which[11–21] were done after publication of the previous global estimates (table 1).[22] These estimates

have important limitations, however. They are based on data from only a few countries, with only one study providing data from Africa. Placebo groups from typhoid vaccine trials were included, and vaccine trials are usually done in areas with high disease burden. Some assumptions used also merit consideration. An adjustment factor of two was used to account for the low sensitivity of blood culture. A conservative case-fatality rate of 1% was chosen on the basis of conservative estimates of hospital based typhoid fever studies. Further, there are important consequences of typhoid fever related to absenteeism from work and need for admission, which were not considered.

Where typhoid is endemic, most cases in health facilities are children aged 5–19 years and young adults. Recent population based studies from India, Indonesia, and Vietnam suggest that in some settings typhoid fever is also common in 1–5 year-old children (table 2).[15,17,19,20] Data from hospital-based studies in Bangladesh and Thailand[23,24] support these findings. Surveillance data

Search strategy and selection criteria

We searched MEDLINE, PubMed, EMBASE, and the Cochrane Library from 1995 to 2004 to identify recent studies on the causative organism, disease burden, transmission, risk factors, pathogenesis, diagnosis, treatment, and prevention of typhoid and paratyphoid fevers. The main search terms were "typhoid fever", "paratyphoid fever", "enteric fever", and *Salmonella* in combination with "Typhi" or "Paratyphi". No language restrictions were applied. We mainly selected articles in the past 5 years, but did not exclude commonly referenced and highly regarded older reports. We also searched the reference lists of articles identified by this search strategy. Of all articles identified, 1253 were reviewed for inclusion by two of us (RB and SB). Selection criteria included a judgment about the novelty and importance of studies and their relevance for the well-informed general clinician. Several review articles were included because they provide comprehensive overviews that are beyond the scope of this Seminar.

	Type of surveillance	Age (years)	n	Incidence per 100 000 per year
Urban				
Chile[11]	Passive	5–19	21 904	107
Chile[12]	Passive	5–19	27 305	227
Chile[13]	Passive	5–19	10 302	91
China[14]	Passive	5–19	65 984	22
Indonesia[15]	Passive	3–44	10 268	810
India[16]	Passive	0–40	Not reported	290
India[17]	Active	0–40	6454	980
South Africa[18]	Active	5–16	11 691	850
Rural				
Vietnam[19]	Passive	0–>50	28 239	198
Vietnam[20]	Active	2–4	6017	414
Nepal[21]	Active	5–44	3450	655

Table 1: Incidence of culture-proven typhoid fever from population-based studies in urban and rural settings, published after 1986

from the USA indicate that the proportion of cases of typhoid is constant over the first 25 years of life.[4] Typhoid fever is more common in urban than in rural areas, but studies from two rural settings in Nepal and Vietnam also found a high disease burden.[19–21] Most cases in developed countries arise in travellers, but domestically acquired disease is still reported.[25,26] A total of 1393 typhoid cases were reported between 1994 and 1999 in the USA, 74% of which were related to travel and the rest of which were acquired domestically; 7% of total cases were part of recognised outbreaks.[27]

Paratyphoid fever is estimated to have caused an additional 5·4 million illnesses in 2000.[4] This number is based on an estimated one case of paratyphoid fever for every four cases of typhoid fever (table 3).[11,12,14–16,19,28] Studies from India and Nepal suggest that in some settings and times, paratyphoid fever caused by *S paratyphi A* can contribute up to half of all cases of typhoid fever.[17, 29–31]

About 10% of people recovering from untreated typhoid fever may excrete *S typhi* in the stools for at least 3 months. Between 1% and 5% of typhoid patients become chronic carriers (defined as excretion of *S typhi* in urine or stools for more than one year), and the rate is

	Type of surveillance	Age (years)	n	Incidence per 100 000 per year
Urban				
Indonesia[15]	Passive	3–6	1592	1307
		7–19	4711	1172
		20–44	3965	182
India[17]	Active	0–4	1027	2730
		5–19	2743	1170
		20–40	2684	110
Rural				
Vietnam[19]	Passive	2–4	Not reported	358
		5–9		531
		10–14		429
		15–19		153
		20–29		149
		30–39		51
Vietnam[20]	Active	2–4	6017	414

Table 2: Age-specific incidence of culture-proven typhoid fever from population-based studies

higher for women, those older than 50 years, and patients with schistosomiasis, cholelithiasis, carcinoma of the gall bladder, and other gastrointestinal malignancies.[32] Most chronic carriers are asymptomatic and almost a quarter may have had no history of typhoid fever.

Transmission and risk factors

People are the only natural host and reservoir for *S typhi*. The pathogen can survive for days in groundwater, pondwater, or seawater, and for months in contaminated eggs and frozen oysters.[33–36] The infectious dose is between 1000 and 1 million organisms given orally.[37] The infection is transmitted by ingestion of food or water contaminated with faeces. Established risk factors are contaminated water supply, eating ice cream, flavoured iced drinks or food from street vendors, and raw fruit and vegetables grown in fields fertilised with sewage.[32,38–42] Other reported risk factors include a history of contact with other patients before illness, not using soap for washing hands, poor housing, and past evidence of infection with *Helicobacter pylori*[28,42–44] The mechanism of increased risk of typhoid in individuals with chronic *H pylori* infection is postulated to be reduced gastric acidity. Factors within the household (eg, poor personal hygiene and housing) might be more important risk factors for typhoid, whereas factors outside the household (eg, food from street vendors, flooding) are more important for paratyphoid fever.[28] A possible reason proposed for this difference was the higher infective dose necessary for paratyphoid, which is more likely to be present in food from street vendors. Although chronic typhoid carriers are important for survival of the pathogen, they are less important as a direct source of infection in endemic areas than contaminated water or food.[32–46] In the USA, up to 30% of infections are due to exposure from previously or newly diagnosed chronic carriers.[47]

Involvement of host genetic factors has also been implicated in the pathogenesis of typhoid fever. Work on typhoid fever patients in Vietnam has suggested an important role of HLA-linked genes in governing susceptibility or resistance to this infection. HLA-DRB1*0301/6/8, HLA-DQB1*0201-3, and tumour necrosis factor a (TNFA*2-308) were associated with susceptibility to typhoid fever, and HLA-DRQB1*04 and HLA-DQB1*0401/2 and TNFA*1(-308) were associated with lower risk.[48] HLA-DRB1*12 is associated with protection against complicated typhoid fever.[49] Similar studies in other ethnic groups might help in defining the common HLA genes and the locus of susceptibility.

The pathogen

The causative organism of typhoid fever, belongs to the family Enterobacteriaciae. Most *S typhi* isolates from typhoid fever cases have a polysaccharide capsule (Vi), which is associated with increased infectiousness and virulence, but Vi-negative strains can also cause the

	Type of surveillance	Age (years)	n	Incidence per 100 000 per year	Ratio of typhoid to paratyphoid cases*
Vietnam[19]	Active	2–4	6017	22	18·7
China[14]	Passive	5–19	65 984	5	4·6
Indonesia[15]	Passive	3–44	10 268	187	4·3
Chile[11]	Passive	5–19	21 904	26 (paratyphi B)	4·1
Chile[12]	Passive	5–19	27 305	37 (paratyphi B)	6·2
Indonesia[28]	Passive	1–80	Not reported	Not reported	3·4
India[16]	Active	0–40	6454	372	2·6

*Ignoring Vietnamese study in 2–4 year-old children,19 population-based studies report 2·6–6·2 (median 4·2) cases of typhoid fever for each case of paratyphoid fever. These data justify assumption used in global burden estimates[4] that incidence of paratyphoid fever is about a quarter of that of typhoid fever.

Table 3: Incidence of culture-proven paratyphoid fever from population-based studies

disease.[50] Molecular typing techniques show that many different strains are in circulation in endemic areas but outbreaks are related to a few strains.[51–53] Genetic variation between isolates has been related to clinical outcome. Multidrug resistant isolates, for instance, might be more virulent than sensitive strains,[54] and isolates from fatal cases might be different from background strains.[55]

The complete DNA sequence of a multidrug resistant isolate of *S typhi* isolate, CT18, shows the number of predicted genes to be 4599.[56] The core region conserved between species (70–80% of the chromosome) could represent a gene repertoire associated with basic functions in the Enterobacteriaceae, such as intestinal colonisation, survival in the environment, and transmission. Scattered along this conserved core are single genes or groups of genes that are specific to *S enterica* or indeed to serotype typhi. Up to ten *Salmonella* pathogenicity islands have been identified. All types of *S enterica* have two large clusters of genes known as *Salmonella* pathogenicity island 1 (SPI-1) and SPI-2, that facilitate invasion of and survival inside host cells. The *S typhi* genome also contains SPI-7, which has genes that code for Vi polysaccharide production as well as many other genes of unknown function. There are more than 200 pseudogenes that have clearly been inactivated by simple point mutations or frameshifts, 145 of them are present as active genes in *S typhimurium*. Significantly, *S typhimurium* causes a different disease in people, and has a wider host range than *S typhi*.[56,57] Two plasmids are present—a larger transmissible one called pHCM1 that encodes several drug-resistance determinants, and a smaller one, pHCM2, which is phenotypically cryptic.[57,58]

Sequence and microarray analysis of the genome of *S paratypi A* indicates that it is similar to that of *S typhi*, but that it might have a more recent evolutionary origin. It has accumulated 173 pseudogenes by comparison with about 210 of the *S typhi*.[59]

Pathogenesis

S typhi, unlike *S typhimurium*, avoids triggering of an early inflammatory response in the gut of the human host, using a stealth approach to allow colonisation of deeper tissues of the body.[2,60] The description of typhoid fever pathogenesis we provide is based largely on the murine model in which *S typhimurium* causes a systemic infection similar to typhoid.

S typhi probably invades the gut mucosa in the terminal ileum through specialised antigen-sampling cells, known as M-cells, which overlie gut-associated tissue,[61] through enterocytes, or via a paracelluar route.[62] The bacteria adhere to the intestinal mucosa in the terminal ileum through interaction with an epithelial receptor, the cystic fibrosis transmembrane conductance regulator protein.[63] A key, early step in the infectious process is the induction of intestinal epithelial cells to increase membrane receptor levels, with enhanced bacterial ingestion and submucosal translocation.[64]

Studies of non-typhoidal *Salmonella* spp indicate that invasion of non-phagocytic epithelial cells occurs through the activity of bacterial proteins delivered into host cells by a type III secretion system, encoded on SPI-1.[65–67] The formation of an intracellular replicative niche requires further activity of SPI-1,[68] which is downregulated after a few hours of invasion,[69] followed by activity of a second type-III secretion system, encoded on SPI-2.[70,71]

The bacterial invasion leads to infiltration of peripheral blood leucocytes into the lamina propria. This infiltration is mediated by cytokine secretion from epithelial cells induced by bacterial lipopolysaccharide, a component of the cell wall of gram-negative bacteria. Lipopoly-saccharide activates transcription factors in lymphocytes by signalling through a mammalian Toll pathway known as Toll-like receptor 4 complex.[72,73] Invading bacteria are taken up by macrophages, which undergo salmonella-induced caspase-1 mediated apoptosis.[57]

The bacteria reach the intestinal lymphoid tissue, and are drained into mesenteric nodes, the thoracic duct, and then the general circulation. This primary bacteraemia results in the organism reaching the liver, spleen, bone marrow, and other parts of the reticuloendothelial system within 24 h of their ingestion, where they survive and replicate in cells of monocytic lineage.[74] Bacteria are shed back into the bloodstream, marking the onset of the clinical illness (after an incubation period of 8–14 days) during which a low level of bacteraemia is sustained.
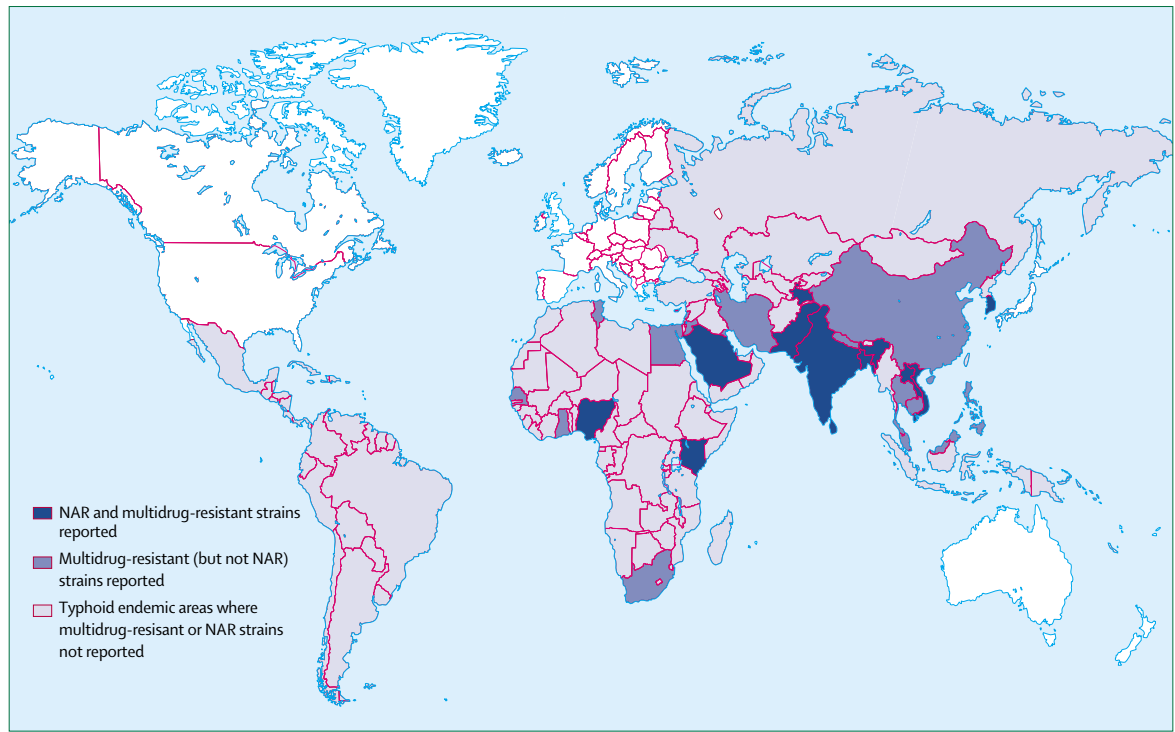
***Figure:* Global distribution of antimicrobial resistance in *S typhi* (1990–2004)**
Adapted from Parry and colleagues[96] and updated on basis of data from past 3 years.

A possible underlying molecular mechanism for persistence of salmonella in the host, as seen in typhoid carrier state, has been proposed.[2] Differences in mouse susceptibility to *S typhimurium* have been linked to the particular allele of the *Nramp*1 gene expressed on their macrophages.[75] *Nramp*1 is involved in controlling exponential growth of salmonella in the reticuloendothelial system during the early stages of infection. Mice expressing the wildtype *Nramp*1 allele did not die after oral inoculation with *S typhimurium*, but became uniformly persistently infected as did chronic typhoid carriers.[76] Salmonella persisted in small numbers, mainly in the macrophages of mesenteric lymph nodes or spleen (or both), despite a robust antibody response. Reactivation of intracellular salmonella and systemic spread could be accomplished by administering antibodies to neutralise interferon γ, suggesting that host cytokine interferon γ is important for suppression of salmonella replication and disease.

Antimicrobial resistance

In late 1987, there was an outbreak of typhoid fever in China caused by strains resistant to all the first line antimicrobials (ampicillin, co-trimoxazole, and chloramphenicol).[77] During 1989–1990, there were reports of similar *S typhi* strains from India, Pakistan, and the Arabian Gulf.[78–80] Such multidrug resistant typhoid is now reported from many parts of the world (figure).[38,39,53,54,81–94] Multiple antimicrobial resistance is mediated through pHCM1 plasmid,[95,96] which has 99% sequence identity with plasmid R27,[97] an *inc* H1 plasmid.[95] For at least 74% of the isolates in Vietnam, endemic and epidemic multidrug-resistant typhoid fever was due to one or two clones of *S typhi* carrying a single resistance plasmid.[98]

A decreasing trend has been reported in the isolation of multidrug-resistant *S typhi* strains from southern Asia. In a retrospective analysis of blood cultures in a diarrhoea treatment centre in Bangladesh,[99] the rate of multidrug-resistant *S typhi* was 0·3% of all blood cultures in 1990, a peak of 3·2% in 1994, and 1·0% in 1996. The isolation rate of susceptible *S typhi* remained remarkably unchanged (3·3%) during the study. More than 90% of *S typhi* strains isolated in 1999 from typhoid patients in a hospital in New Delhi were sensitive to chloramphenicol.[100] In another study from India,[101] all *S typhi* isolates were resistant to chloramphenicol in 1991, but chloramphenicol resistance fell to less than 20% by 2000.[101]

After emergence of multidrug resistance, fluoroquinolones (eg, ciprofloxacin, ofloxacin) became the treatment of choice for typhoid fever. Isolates fully susceptible to ciprofloxacin by disc testing typically have a ciprofloxacin minimum inhibitory concentration of less than 0·03 mg/L and are invariably also susceptible to the first generation quinolone nalidixic acid. A population of isolates exists with a minimum inhibitory concentration of 0·125–1·0 mg/L that seems to be susceptible to

ciprofloxacin by disc testing but is associated with clinical failure and is resistant to nalidixic acid (NAR strains); such isolates have been reported from several countries (figure).[25,83,84,94,102–108] Single point mutations (Ser-83 to Phe, Asp-87 to Asn, Ser-83 to Tyr and Asp-87 to Gly) in the gyrA gene of *S typhi* and *S paratyphi* cause this reduced susceptibility to ciprofloxacin.[103,107,109,110] Table 4 summarises key features of NAR isolates.[107,108,111,112] The National Committee for Clinical Laboratory Standards currently recommends testing of extraintestinal salmonella isolates for nalidixic acid resistance as a marker for reduced fluoroquinolone susceptibility.[113] This testing is, however, not foolproof—in Europe, 11% of *S typhi* strains with decreased ciprofloxacin susceptibility were sensitive to nalidixic acid.[114] Multidrug resistance as well as reduced susceptibility to ciprofloxacin has also been reported for *S paratyphi A*.[115]

Laboratory diagnosis

Confirmation of typhoid or paratyphoid fever requires isolation of *S typhi* or *S paratyphi*, respectively, from blood, bone marrow, stool, or duodenal fluid. Cultures from skin above rose spots, buffy coats, and blood clots treated with streptokinase have been used.[116–119] Bone-marrow aspirate culture is positive in 80–95% of typhoid patients.[116–118,120] Culturing more than 10 mL of blood is necessary to match the positivity rate with that of 1 mL of bone marrow. Bone-marrow cultures are useful for lengthy illness and antibiotic treatment.[118,121,122] Blood culture is the mainstay of diagnosis. Using standard broth cultures, salmonella is isolated in 30–90% of patients with clinical typhoid.[118,121,122] Sensitivity decreases with increasing duration of fever.[118] The volume of blood and the ratio of blood to broth determines blood culture yield: 10–15 mL of blood is necessary to maintain an optimum ratio of 1 to 12. 2–4 mL of blood is sufficient in children who have a greater concentration of bacteria in their blood.[122,123] Failure to maintain ambient temperatures of 15–40°C during specimen transportation, inappropriate laboratory methods, and antimicrobials compromise the yield.

Stool isolation of *S typhi* alone is insufficient for diagnosis and only marginally improves diagnosis by blood culture. However, it is confirmatory for carrier detection. Serological tests based on agglutination of Vi antigens have 70–80% sensitivity and up to 95% specificity in identifying carriers of *S typhi*.[124]

The Widal test identifies the agglutinating antibodies against the O (somatic) and H (flagellar) *S typhi* antigens, which appear a week to 10 days after disease onset. The sensitivity, specificity, and predictive values reported from different centres vary because of sharing of O and H antigens and cross-reacting epitopes with other Enterobacteriaceae.[125] The high number of false-positive and false-negative Widal test results limit its clinical usefulness. To make a diagnosis, results from a single acute sample should be interpreted against the

	Proportion of NAR strains	% patients who failed on fluoroquinolone treatment	% cases with faecal carriage during early convalescence
UK[111]	23% (42/179)	24% (10/42)	Not reported
Canada[112]	33% (7/21)	80% (4/5)	Not reported
India[107]	47% (82/174)	27% (22/82)	Not reported
Vietnam[108]	9% (46/504)	24%* (11/46)	21%† (8/39)

*By comparison, 5% (22/458) of nalidixic-acid-sensitive strains had clinical failure on ofloxacin. †By comparison, 2% (7/383) of nalidixic-acid-sensitive strains had faecal carriage during early convalescence.

Table 4: Key features of nalidixic-acid-resistant (NAR) strains of *S typhi*

appropriate local cut-off values or there should be a four-fold rise in the antibody titres between convalescent and acute sera.[126,127]

Some simple inexpensive rapid serological diagnostic tests for typhoid fever are available (table 5).[128–133] In an evaluation of three commercial kits, the sensitivity and specificity for identifying blood-culture-positive cases of typhoid fever was 89% and 53% for multi-test dip-sticks (PANBIO INDX, Baltimore, MD, USA), 79% and 89% for typhidot (Malaysian Biodiagnostic Research SDN BHD, Malaysia), 78% and 89% for tubex test (IDL Bideh, Solletuna, Sweden) as compared with 64% and 76% for Widal.[128]

The understanding of genome sequence of *S typhi* might now result in identification of specific antibodies to fimbrial and other antigens.[57] Urinary Vi antigen detection by ELISA within the first febrile week shows promise, but positivity in brucellosis patients is an obstacle to further development.[134] DNA probes and PCR-based tests to detect flagellar genes[135] are not routinely useful in developing countries, but they are of value in surveillance and research.

Clinical features

The clinical presentation of typhoid fever is very variable, ranging from fever with little other morbidity to marked toxaemia and associated complications involving many systems. In endemic regions, diagnosis can be missed because of non-specific features like diarrhoea and vomiting, or predominant respiratory symptoms.[17,19] Because of this variable profile, the disease has to be differentiated from tuberculosis, brucellosis, sepsis due to other bacterial pathogens, infectious mononucleosis, anicteric hepatitis, and, infrequently, from leukaemia and lymphoma. In the days when chloramphenicol was clinically effective, typhoid fever was largely treated on an outpatient basis, but with the emergence of multidrug-resistant strains and decreased susceptibility to fluoroquinolones, it has acquired a profile of severe infectious disease that often requires inpatient care. In developing countries, admission has substantial consequences for poor families.

An average case of acute non-complicated typhoid fever has an incubation period of 10–14 days and is usually associated with prolonged low-grade fever, dull frontal headache, malaise, myalgia, a dry bronchitic

	Antibodies	Country	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Tubex S typhi O9 antigen	Immunoglobulin M	Vietnam[129]*	87%	76%	77%	84%
Dipstick S typhi Lipopolysacchride antigen	Immunoglobulin M	Vietnam[129]*	48%	98%	99%	65%
	Immunoglobulin G	Vietnam[128]†	89%	50%	83%	60%
	Immunoglobulin M	Indonesia[130]†	65·3%	100%	100%	61%
	Immunoglobulin M	Indonesia[131]†	86·5%	88·9%	90·4%	66·6%
Typhidot Dot-ELISA S typhi 50 $_R$D OMP	Immunoglobulins G or M	Vietnam[128]†	79%	89%	96%	59%
	Immunoglobulins G or M, alone or in combination	Pakistan[132]*	94%	77%	88%	87%
	Immunoglobulins G + M	India[133]†	100%	80%	83·3%	100%
Typhidot M Dot-ELISA S typhi 50 $_R$D OMP	Immunoglobulin M	Pakistan[132]*	73%	89%	95%	55%

Studies only included where the gold standards were positive blood or bone-marrow culture (*) or positive blood culture (†). OMP=outer membrane protein.

Table 5: Performance of new diagnostic tests for typhoid fever

cough, anorexia, and nausea. The fever might rise progressively in a stepwise manner to become persistent and high grade by the second week of illness.[46] Continuous high-grade fever can continue for up to 4 weeks if left untreated, followed by a return to normal temperature. Malaise and lethargy can continue for a couple of months later.

Although not present consistently, relative bradycardia at the peak of high fever is an indicator of typhoid fever. Coated tongue, alteration of bowel habits varying from constipation in adults to diarrhoea in children, tender abdomen, hepatomegaly, and splenomegaly are often present.[96,136] Small erythematous maculopapular lesions (rose spots) are seen on the back, arms, and legs in up to a quarter of cases late in the first week of fever, particularly in fair-skinned people. Rhonchi and scattered crepts might be heard on chest auscultation. Liver involvement is common with elevated concentrations of serum bilirubin and alanine transferase; in endemic areas, typhoid fever should be a differential diagnosis for a patient with fever and jaundice.[137]

Neonatal typhoid fever resulting from vertical transmission during late pregnancy is a rare but often life-threatening illness. It usually begins during 3 days of delivery with fever, vomiting, diarrhoea, and abdominal distension. There might be significant hepatomegaly and jaundice. Seizures can occur. It could also present as asymptomatic persistent excretion. In children younger than 5 years, typhoid fever can be milder and can mimic a viral syndrome. The rate of severe complications is lower than at later ages.[17,138]

Overall, about 10–15% of patients develop severe disease. Factors affecting severity include duration of illness before therapy, choice of antimicrobial therapy, strain virulence, inoculum size, previous exposure or vaccination, and other host factors such as HLA type, AIDS or other immune suppression, or antacid consumption. The commonest complications are gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.[46,96] A rapid drop in temperature during the later period of the illness suggests intestinal bleeding or perforation. This drop is usually followed by a rise in temperature after a few hours as peritonitis develops. Gastrointestinal bleeding occurs in 10–20% of cases due to erosion of the Peyer's patch into an intestinal vessel and is usually restricted to either occult blood in stool or malaena. On colonoscopy, terminal ileum is the commonest site involved followed by the ileocaecal valve, the ascending then the transverse colon.[139] Multiple punched out ulcers with slightly elevated margins are evident.

Intestinal perforation occurs in 1–3% of cases in hospital; the commonest site is the ileum.[140] Being male, leucopenia, inadequate treatment before admission, and short duration of symptoms are significant predictors of perforation.[141] Intermittent confusion, insomnia, and dizziness are reported in 3–10% of cases and these symptoms are associated with high case fatality. Some patients manifest neuropsychiatric symptoms such as picking at bedclothes or imaginary objects, which are described as muttering delirium or coma vigil. Deep coma is rare. Typhoid meningitis, encephalomyelitis, Guillain-Barré syndrome, and cranial or peripheral neuritis have been reported from different regions with incidence of 2–40%. Convulsions occasionally arise in young children.[142] Examination of the cerebrospinal fluid

is recommended in patients with behavioural or neurological manifestations and negative blood cultures to rule out tubercular meningitis.

Severe complications such as disseminated intravascular coagulation or haemorrhages can lead rapidly to death. Severe pneumonia is more frequent in children than adults. The other rare complications reported include hepatic, splenic, and bone-marrow granulomas, splenic and liver abscesses, pleural effusion, multiple organ dysfunction syndrome, haemato-phagocytic syndrome, pseudotumour cerebri, haemolytic uraemic syndrome, glomerulonephritis or pylonephritis, endocarditis, and pericarditis.[143–147] Arrhythmia or cardiogenic shock can be a manifestation of toxic myocarditis with fatty infiltration of the heart.

With the introduction of early and appropriate antibiotic therapy, the average case fatality rates for typhoid are less than 1%; however, mortality as high as 30–50% has been reported from Papua New Guinea and Indonesia for severe typhoid fever.[148,149] In 552 culture-positive patients with typhoid fever in hospital in Bangladesh, the overall case-fatality rate was 4·3%, with the highest rates for those younger than 1 year (11%) and for adults 31 years or older (10%).[142] Further, 5–10% of cases can relapse after 2–3 weeks of resolution of the initial fever, but the clinical severity of this episode is much lower. Relapse can happen without a history of therapeutic intervention but more often it follows antibiotic treatment.[150–152] The incidence of relapse after treatment with fluoroquinolones (1·5%) or broad-spectrum cephalosporins (5%) is lower than that after treatment with chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin.[153] Most relapses are caused by the same *S typhi* strain with the same antibiotic susceptibility patterns as the initial episode. However, some individuals become reinfected with distinct and possibly newly acquired isolates.[153]

Clinical features of paratyphoid fever are similar to those of typhoid fever but are usually milder with a shorter incubation period. *S paratyphi A* or *paratyphi B* can manifest with jaundice, thrombosis,[154,155] and systemic infections.[156] *S paratyphi B* might occasionally have an onset similar to non-specific salmonella gastroenteritis. Gastrointestinal symptoms are usually not present with *S paratyphi C* but there have been cases with systemic complications such as septicaemia and arthritis.[157] A relapse rate of 8% has been reported with *S paratyphi A*.[158]

Treatment

Important considerations for treatment are the prevention of severe complications and death, and prompt resolution of clinical disease. It is also important to eradicate the organism promptly to prevent relapses and faecal carriage. More than 90% of patients are managed at home with oral antimicrobials, bedrest, and close medical follow up. Patients with persistent vomiting, severe diarrhoea, or abdominal distension need admission to hospital and parenteral antibiotic therapy.[46]

Typhoid fever should be a serious consideration in an endemic area when a fever lasts longer than a week, even by the fifth day if there is severe toxaemia. The decision to send laboratory investigations and initiate empirical antimicrobial therapy depends largely on clinical judgment. Initial choice of antibiotic depends on the sensitivity patterns of *S typhi* and *paratyphi* isolates in the area. The isolates can be broadly classified as sensitive to first-line antimicrobials, multidrug resistant but nalidixic-acid sensitive, and nalidixic-acid resistant (often also multidrug resistant).

Fluoroquinolones (ciprofloxacin, ofloxacin, and pefloxacin) are the most effective drugs for treatment of

	First-line oral drug			Second-line oral drug		
	Antibiotic	Daily dose (mg/kg)	Days	Antibiotic	Daily dose (mg/kg)	Days
Uncomplicated typhoid at home						
Fully susceptible	Fluoroquinolone	15	5–7	Chloramphenicol	50–75	14–21
				Amoxycillin	75–100	14
				Trimethoprim -sulpfamethoxzole	8 (trimethoprim) 40 (sulfamethoxazole)	14
Multidrug-resistant	Fluoroquinolone	15	5–7	Azithromycin	8–10	
				or cefixime	20	7 7–14
Nalidixic-acid resistant	Azithromycin or cefixime	8–10 20	7 7–14	Fluoroquinolone	20	10–14
Severe typhoid in hospital						
Fully susceptible	Fluoroquinolone	15	10–14	Chloramphenicol	100	14–21
				Ampicillin	100	10–14
Multidrug-resistant	Fluoroquinolone	15	10–14	Ceftriaxone or cefotaxime	60 80	10–14
Nalidixic acid resistant	Ceftriaxone or cefotaxime	60 80	10–14	Fluoroquinolone	20	10–14

Adapted from Parry and colleagues.[96]

Table 6: Antibiotic treatment for typhoid

typhoid fever caused by isolates that are not quinolone resistant,[159–163] with a clinical cure rate of about 98%, fever clearance time of about 4 days, and relapse and faecal carriage rates of less than 2%.[96] Chloramphenicol, the traditional first-line drug of choice, is less effective than fluoroquinolones in all these respects and in terms of persistence of the organism in bone marrow, even for treatment of patients with fully sensitive isolates.[96,164]

Fluoroquinolones are equally effective for treatment of typhoid fever in children and adults.[165] However, these drugs are not registered for routine use in children because of evidence of articular damage in growing, weight-bearing joints in young beagles.[166,167] Extensive experience of these drugs in children with typhoid, cystic fibrosis, and dysentery has shown no evidence of bone or joint toxicity, and impairment of linear growth.[168–172] Where multidrug resistant strains are common and third-generation cephalosporins unavailable, fluoro-quinolones can be used for treatment of typhoid fever in children.

Short courses of ofloxacin given for 2, 3, or 5 days treated more than 90% of patients infected with multidrug resistant but nalidixic-acid susceptible isolates of *S typhi*, with an average fever clearance time of 4 days. Less than 3% of patients relapsed or had a positive posttreatment stool culture. Such short-term regimens are especially useful in control of epidemics. By contrast, the response of NAR isolates to such regimens is poor. Ofloxacin given for 7 days cured only 75% of patients infected with NAR isolates with a fever clearance time of 7 days, and 19% patients had a positive posttreatment stool culture.[103,108]

Azithromycin, and cefixime, an oral third-generation cephalosporin, have a clinical cure rate of over 90% with a fever clearance time of 5–7 days and relapse and faecal carriage rates of less than 4% in typhoid fever.[108,161–163,173–176] These antimicrobials are therefore regarded as acceptable therapy for quinolone-resistant typhoid and paratyphoid fever. Their major limitations are high cost and low availability (table 6).

Combinations of antimicrobials are being assessed to provide more affordable options for treatment of quinolone-resistant typhoid fever. Ciprofloxacin proved to be more effective in combination with amoxycillin than ciprofloxacin alone against *S typhi* strains in vitro with a ciprofloxacin minimum inhibitory concentration of 1 mg/L or more.[177] The fractional inhibitory concentration for ciprofloxacin against these isolates was 0·004–0·256 mg/L when the antibiotic combination was used.[177] Similar findings have been reported for a combination of ciprofloxacin and gentamicin.[178]

Supportive treatment includes maintenance of hydration, appropriate nutrition, and antipyretics. In a recent study, children with uncomplicated typhoid fever were randomly assigned to receive either ibuprofen or paracetamol every 6 h until 36 h after defervescence.[179] Median fever clearance time was shorter with ibuprofen

as was the area under the temperature–time curve above 37ºC. The differences were mainly in children infected with NAR *S typhi* who responded slowly to antibiotic treatment.

Severe typhoid and paratyphoid

Patients with persistent vomiting, severe diarrhoea or abdominal distension requiring admission, and those with complications should be treated for severe typhoid fever. Fluoroquinolones remain the antibiotic of choice in areas where prevalence of quinolone-resistant isolates is low even though there have been no randomised antibiotic trials in patients with severe typhoid.[165] Third-generation cephalosporins (ceftriaxone or cefotaxime) are recommended where quinolone resistant isolates are prevalent (table 6). Antimicrobials should be given parenterally for at least 10 days, or for at least for 5 days after defervescence.[180,181] In Pakistan, clinical and bacteriological cure rates were similar with 7-day or 14-day treatment with intravenous ceftriaxone, but the confirmed bacteriological relapse rates were 14% with the 7-day regimen whereas none in the 14-day treatment group relapsed.[187]

In Indonesian adults and children with delirium, obtundation, stupor, coma, or shock, mortality was reduced from 50% to 10% for those given dexamethasone as an initial dose of 3 mg/kg by slow intravenous infusion over 30 min followed by 1 mg/kg at the same rate every 6 h for eight additional doses.[148,183]

Patients with intestinal haemorrhage need intensive care, monitoring, and blood transfusion when blood loss is substantial. Patients with intestinal perforation should be resuscitated with fluids or blood and undergo early surgical intervention within 6 h to prevent death.[46] Relapses should be treated in the same way as initial infections.

Treatment of chronic carriers

Most carriers (defined as individuals who excrete *S typhi* in their stools or urine for more than a year) without gallstones can be cured by a long course of antimicrobials. Almost 80% of carriers were cured by 750 mg of ciprofloxacin twice daily for 28 days, and 11 out of 12 carriers treated with 400 mg norfloxacin twice daily had negative stool and bile cultures for *S typhi* after 28 days of treatment.[184,185] In patients with gallstones, cholecystectomy along with antibiotic therapy might be required. Carriers should be excluded from any activities involving food preparation and serving, as should be people recovering from typhoid fever.

Prevention

The key preventive strategies are safe water, safe food, personal hygiene, and appropriate sanitation.[46] The importance of prevention has greatly increased with the emergence of antibiotic resistance. However,

provision of safe water and appropriate sanitation are expensive and are usually linked with economic development. Vaccination is an additional effective tool for prevention of typhoid fever. Vaccination is useful for prevention of typhoid in travellers from developed countries to typhoid endemic countries, in preventing and controlling epidemics, as well for children in endemic settings aged 2–19 years.[46]

Most cases of typhoid fever in developed countries are a result of travel to endemic disease areas. Six countries—India, Pakistan, Mexico, Bangladesh, the Philippines, and Haiti—accounted for 76% of travel associated cases.[186] 37% of these cases were in people who stayed at their travel destination for 4 weeks or less and 16% were in people who stayed for 2 weeks or less. 80% cases were in people visiting relatives and friends. Travellers to these countries, especially those visiting for 2 weeks or more and those visiting friends and relatives, should be targeted for vaccination.

The old parenteral whole-cell typhoid-paratyphoid A and B vaccine was effective against both typhoid and paratyphoid fevers but has been largely discontinued because of strong side-effects.[187] Two vaccines for typhoid fever, one based on Vi polysaccharide and the other on whole-cell live attenuated bacteria, are currently licensed. A new Vi-conjugate vaccine is highly effective in children younger than 5 years but it has not been tested in infants. Currently, there is no licensed vaccine for paratyphoid fever.

Vi polysaccharide vaccine
This vaccine is licensed for use in individuals older than 2 years and is given in a single subcutaneous or intramuscular dose. The vaccine is moderately effective for about 3 years after vaccination (table 7).[14,21,188,189] Revaccination is recommended every 3 years. However, 58% of participants in a field trial in South Africa still had protective levels of antibodies 10 years after vaccination.[192] This vaccine has shown about 70% protective efficacy in a population vaccinated before or during an outbreak in China.[189] The Vi vaccine can be given simultaneously with other vaccines relevant for international travellers such as yellow fever and hepatitis A.[190,191,193]

Ty21a vaccine
This live oral vaccine available in enteric-coated or liquid formulation is approved for use in people 6 years of age and older. The liquid formulation for younger children is currently marketed in only a few countries. Three doses are recommended each given 2 days apart. Antimicrobials should be avoided for 7 days before or after vaccination. The vaccine is moderately effective for up to about 3 years after vaccination (table 7).[11–13,15,194,195] A booster dose is recommended every 3 years in endemic areas and travellers should be revaccinated annually. Herd immunity was shown during field trials in

	Age range (years)	Follow up (years)	Dose	Protective efficacy (95% CI)
Vi vaccine				
Nepal[21]	5–44	1·5	Single dose	72% (41–87)
South Africa[186]	5–16	3	Single dose	55% (30–71)
China[14]	3–19	1·5	Single dose	69% (28–87)
China[187]	12–21	Immunised during epidemic or up to 1 year earlier	Single dose	71% (34–87)
Ty21a vaccine				
Egypt[194]	6–7	3	3 doses (enteric coated capsules)	96% (67–99)
Chile[11]	6–21	3	3 doses (enteric coated capsules)	67% (47–79)
Chile[13]	5–19	3	3 doses (enteric coated capsules)	33% (0–57)
			3 doses/liquid	77% (60–87)
Chile[12]	5–22	2	2 doses (enteric coated capsules)	59% (41–71)
Chile[195]	6–19	5	3 doses (liquid)	78% (65–87)
Chile[195]	6–19	7	3 doses (enteric coated capsules)	62% (48–73)
Indonesia[15]	3–44	2·5	3 doses (enteric coated capsules)	42% (23–57)
			3 doses (liquid)	53% (33–66)

Table 7: Effectiveness of two typhoid vaccines

Chile.[11,13] The vaccine can be given simultaneously with other vaccines and with antimalarial prophylaxis.[196]

The effectiveness of both these licensed vaccines in developing countries is similar. Ty21a has the advantage that it is given orally and therefore might be easier for immunising groups of children, as in schools. The Ty21a vaccine, especially the enteric-coated capsule formulation, is not licensed for use in 2–5 year-old children. Vi vaccine has a relative advantage that it can be used for these preschool children, in settings where typhoid fever is common in this age-group. The vaccine however, is not licensed for use in children younger than 2 years.

Post-marketing surveillance for typhoid fever vaccines from the Vaccine Adverse Effects Reporting System from 1990 to 2002 has shown rare reports of death, admission, permanent disability, or life-threatening illness.[197] Unexpected frequently reported symptoms included dizziness and pruritis for Vi vaccine and fatigue and myalgia for Ty21a. Gastroenteritis for Ty21a and abdominal pain after Vi vaccine are previously recognised events.

Vi-conjugate vaccine
Vi-conjugate vaccine given to 2–5 year-old Vietnamese children had 91·1% protection against typhoid 27 months after vaccination, with geometric mean titres of 7·61 ELISA units for those vaccinated at age 2–3 years.[20] The efficacy of this conjugate persisted after 46 months of vaccination: over the entire period the protection was 89% (95% CI 76%–97%).[198] Based on the antibody titres after 46 months of vaccination, the researchers suggest a protective level of antibody to immunoglobulin G to be reduced from 7 to 3·52 ELISA units. This vaccine could be used for children younger than 2 years and be incorporated into the Expanded Programme on Immunization immunisation schedules.

Vaccines under development

Vaccines are under development based on outer membrane proteins known as porins and new live oral vaccines (eg CVD 908-htrA and Ty2 candidate vaccines).[199–201] A new vaccine against *S paratyphi A* composed of surface-O-specific polysaccharide conjugated with tetanus toxoid has proved safe and immunogenic.[202] Live typhoid vaccines are being developed as a vector for immunisation against *H pylori*.[203]

Conclusion

Typhoid fever is an important public-health problem in south-central and southeast Asia, the middle east, Africa, and South America, mainly affecting children and young adults. Treatment of typhoid fever is becoming more difficult with multidrug resistant organisms also acquiring some resistance to fluoroquinolones. Fully ciprofloxacin-resistant *S typhi* has not been reported, although full resistance in non-typhoid salmonella has emerged.[204,205] Effective immunisation and non-vaccine based prevention strategies are available and are becoming more important in the face of increasing antibiotic resistance.

S typhi is restricted to human beings. The organism does not persist long in any environmental reservoir after its elimination from local regions. The analysis of individual pseudogene mutations from *S typhi* isolates shows that different isolates harbour the same mutations. This strongly suggests that the organism has emerged only once and cannot readily evolve from other *S typhi* serotypes.[53] Improved sanitation, better diagnostics for early detection and treatment of patients and carriers, and mass vaccination are effective interventions in combating typhoid fever. All these factors indicate that global eradication of typhoid is theoretically possible and merits consideration as a global health issue.

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