Review Article

Medical Progress

Typhoid Fever

Christopher M. Parry, M.B., Tran Tinh Hien, M.D., Gordon Dougan, Ph.D., Nicholas J. White, M.D., D.Sc., and Jeremy J. Farrar, M.B., D.Phil.

TYPHOID fever is a systemic infection with the bacterium *Salmonella enterica* serotype typhi. This highly adapted, human-specific pathogen has evolved remarkable mechanisms for persistence in its host that help to ensure its survival and transmission. Typhoid fever was an important cause of illness and death in the overcrowded and unsanitary urban conditions of the United States and Europe in the 19th century.[1] The provision of clean water and good sewage systems led to a dramatic decrease in the incidence of typhoid in these regions. Today most of the burden of the disease occurs in the developing world, where sanitary conditions remain poor. Reliable data from which to estimate the burden of disease in these areas are difficult to obtain, since many hospitals lack facilities for blood culture and up to 90 percent of patients with typhoid are treated as outpatients. Community-based studies have consistently shown higher levels of typhoid than public health figures suggest. Annual incidence rates of 198 per 100,000 in the Mekong Delta region of Vietnam[2] and 980 per 100,000 in Delhi, India,[3] have recently been reported. According to the best global estimates, there are at least 16 million new cases of typhoid fever each year, with 600,000 deaths.[4] The introduction of chloramphenicol for the treatment of typhoid fever in 1948 transformed a severe, debilitating, and often fatal disease into a readily treatable condition.[5] The emergence of resistance to chloramphenicol and other antimicrobial agents has been a major setback.[6] We now face the very real prospect that untreatable typhoid fever will reemerge.

From the Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom (C.M.P., N.J.W., J.J.F.); the Centre for Molecular Microbiology and Infection, Department of Biological Sciences, Imperial College of Science, Technology and Medicine, London (G.D.); the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam (T.T.H.); the Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (N.J.W.); and the University of Oxford Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam (J.J.F.). Address reprint requests to Dr. Farrar at the University of Oxford Clinical Research Unit, Hospital for Tropical Diseases, 190 Ben Ham Tu, Quan 5, Ho Chi Minh City, Vietnam, or at jeremyjf@hcm.vnn.vn.

Typhoid is usually contracted by ingestion of food or water contaminated by fecal or urinary carriers excreting *S. enterica* serotype typhi. It is a sporadic disease in developed countries that occurs mainly in returning travelers, with occasional point-source epidemics.[7] In endemic areas, identified risk factors for disease include eating food prepared outside the home, such as ice cream or flavored iced drinks from street vendors,[8,9] drinking contaminated water,[10] having a close contact or relative with recent typhoid fever,[8,11] poor housing with inadequate facilities for personal hygiene,[12] and recent use of antimicrobial drugs.[9]

The Bacterium

S. enterica serotype typhi is a member of the family Enterobacteriaciae. The bacterium is serologically positive for lipopolysaccharide antigens O9 and O12, protein flagellar antigen Hd, and polysaccharide capsular antigen Vi. The Vi capsular antigen is largely restricted to *S. enterica* serotype typhi, although it is shared by some strains of *S. enterica* serotypes hirschfeldii (paratyphi C) and dublin, and *Citrobacter freundii*. A unique flagella type, Hj, is present in some *S. enterica* serotype typhi isolates from Indonesia.[13] Phage typing, pulse-field gel electrophoresis, and ribotyping have shown that areas of endemic disease usually have many strains in circulation but that outbreaks are usually due to a restricted number of strains.[14-16]

The Genome

Recently, the complete genome sequence was determined for a multidrug-resistant strain of *S. enterica* serotype typhi (CT18), which was isolated in 1993 from a child with typhoid fever in the Mekong Delta region of Vietnam.[17] The CT18 genome harbors 4,809,037 base pairs with an estimated 4599 coding sequences. The genomes of *S. enterica* serotype typhi CT18, *S. enterica* serotype typhimurium LT2,[18] and *Escherichia coli*[19] are essentially collinear, despite the fact that *E. coli* and *S. enterica* diverged about 100 million years ago. Similar environmental requirements for these enteric bacteria presumably explain this conservation of gene order. Gene clusters unique to particular bacteria are likely to represent adaptations to particular environments or may contribute to pathogenicity. Unlike *E. coli, S. enterica* serotype typhi has several large insertions in its genome, termed salmonella pathogenicity islands, that are thought to be re-

cent horizontal acquisitions and that encode genes important for survival in the host. In addition, there are multiple insertions of many smaller gene blocks and individual genes scattered in the genome that may potentially be involved in pathogenicity (Fig. 1).

A striking feature of the *S. enterica* serotype typhi genome is the presence of 204 pseudogenes, more than half of which are inactivated by the introduction of a single frame-shift or stop codon, suggesting that they are of recent origin. A substantial number are predicted to be involved in housekeeping functions or in virulence or host interactions. This apparent inactivation of genes responsible for host interactions may explain why *S. enterica* serotype typhi, unlike other salmonella serotypes, is restricted to one host (i.e., humans) and suggests that *S. enterica* serotype typhi may have passed through a recent evolutionary bottleneck.

S. enterica serotype typhi CT18 harbors two plasmids. The larger conjugative plasmid, pHCM1, is 218 kb in length and shares approximately 168 kb of DNA with the plasmid R27, with more than 99 percent sequence identity.[20] R27 is an *inc*H1 plasmid, first isolated in the 1960s from *S. enterica*, that is closely related to the chloramphenicol-resistance plasmids detected in *S. enterica* serotype typhi in the 1970s.[21] The pHCM1 plasmid encodes resistance to chloramphenicol (*cat*I), ampicillin (TEM-1, *bla*), trimethoprim (*dhfr*1b), sulfonamides (*sul*II), and streptomycin (*str*AB). The smaller plasmid, pHCM2, is 106.5 kb in length and is phenotypically cryptic, but it has strik-

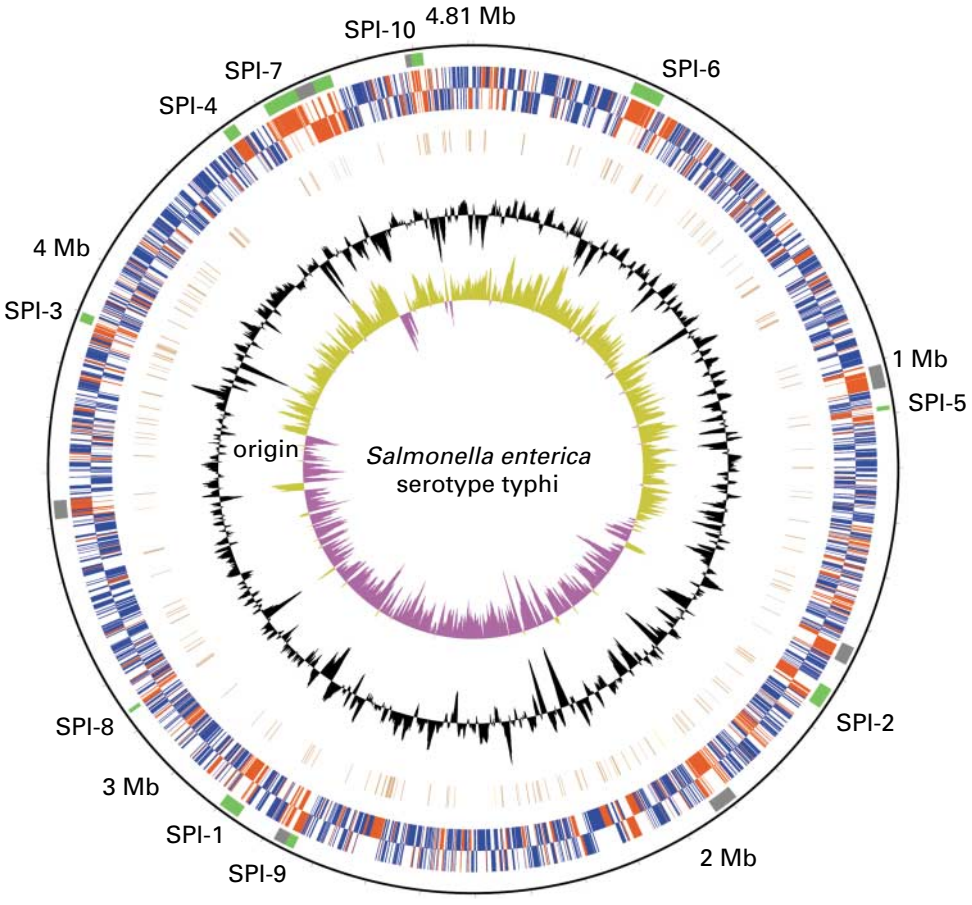

Figure 1. Genetic Similarity of *Salmonella enterica* Serotype Typhi and *Escherichia coli.*

The outer circle shows known and potential salmonella pathogenicity islands (green) and prophage (gray). The next two circles inward show genes conserved between *S. enterica* serotype typhi and *E. coli* (blue) and genes unique to *S. enterica* serotype typhi (red), transcribed in the clockwise and counterclockwise directions. The fourth circle shows pseudogenes in brown. The black circle shows guanine and cytosine (G+C) content graphically, relative to the chromosomal average, and the inner circle graphically shows G/C skew, defined as (G−C)/(G+C). Olive indicates G/C skew of one or more, and purple G/C skew of less than one. (Courtesy of Dr. Julian Parkhill, Sanger Centre, Cambridge, United Kingdom.)

ing homology with the pMT1 virulence-associated plasmid of *Yersinia pestis*.

Pathogenesis

The infectious dose of *S. enterica* serotype typhi in volunteers varies between 1000 and 1 million organisms.[22] Vi-negative strains of *S. enterica* serotype typhi are less infectious and less virulent than Vi-positive strains. *S. enterica* serotype typhi must survive the gastric acid barrier to reach the small intestine, and a low gastric pH is an important defense mechanism. Achlorhydria as a result of aging, previous gastrectomy, or treatment with histamine H_2-receptor antagonists, proton-pump inhibitors, or large amounts of antacids lowers the infective dose. In the small intestine, the bacteria adhere to mucosal cells and then invade the mucosa. The M cells, specialized epithelial cells overlying Peyer's patches, are probably the site of the internalization of *S. enterica* serotype typhi and its transport to the underlying lymphoid tissue. After penetration, the invading microorganisms translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes, and some pass on to the reticuloendothelial cells of the liver and spleen.

Salmonella organisms are able to survive and multiply within the mononuclear phagocytic cells of the lymphoid follicles, liver, and spleen.[23] At a critical point that is probably determined by the number of bacteria, their virulence, and the host response, bacteria are released from this sequestered intracellular habitat into the bloodstream. The incubation period is usually 7 to 14 days. In the bacteremic phase, the organism is widely disseminated. The most common sites of secondary infection are the liver, spleen, bone marrow, gallbladder, and Peyer's patches of the terminal ileum. Gallbladder invasion occurs either directly from the blood or by retrograde spread from the bile. Organisms excreted in the bile either reinvade the intestinal wall or are excreted in the feces. Counts of bacteria in patients with acute typhoid fever indicate a median concentration of 1 bacterium per milliliter of blood (about 66 percent of which are inside phagocytic cells) and about 10 bacteria per milliliter of bone marrow.[24-26] Even though *S. enterica* serotype typhi produces a potent endotoxin, mortality from treated typhoid fever for patients at this stage is less than 1 percent. Studies have shown increased levels of circulating proinflammatory and antiinflammatory cytokines in patients with typhoid and a reduced capacity of whole blood to produce inflammatory cytokines in patients with severe disease.[27-29]

Typhoid induces systemic and local humoral and cellular immune responses, but these confer incomplete protection against relapse and reinfection. The interaction of host immunologic mediators and bacterial factors in infected tissue may contribute to the necrosis of Peyer's patches in severe disease.[30] The evidence for an association between typhoid and infection with the human immunodeficiency virus (HIV) is conflicting,[31,32] whereas there is a large increase in the incidence of non-typhi salmonella bacteremia in HIV infection. Major-histocompatibility-complex class II and class III alleles have been shown to be associated with typhoid fever in Vietnam. HLA-DRB1*0301/6/8, HLA-DQB1*0201-3, and TNFA*2(−308) were found to be associated with susceptibility to typhoid fever, whereas HLA-DRB1*04, HLA-DQB1*0401/2, and TNFA*1(−308) were associated with disease resistance.[33] Polymorphisms in the genes encoding the natural-resistance–associated macrophage protein were not associated with resistance to typhoid, in contrast to the importance of this allele in the murine model.[34]

Antimicrobial Resistance

In 1948 chloramphenicol became the standard antibiotic for treating typhoid.[5] Although resistance emerged within two years after its introduction, it was not until 1972 that chloramphenicol-resistant typhoid fever became a major problem.[6] Outbreaks occurred in Mexico, India, Vietnam, Thailand, Korea, and Peru.[6] Chloramphenicol resistance was associated with high-molecular-weight, self-transferable, *Inc*HI plasmids. These *S. enterica* serotype typhi strains were also resistant to sulfonamides, tetracycline, and streptomycin, but initially amoxicillin and trimethoprim–sulfamethoxazole remained effective alternative drugs. Toward the end of the 1980s and the 1990s, *S. enterica* serotype typhi developed resistance simultaneously to all the drugs that were then used as first-line treatment (chloramphenicol, trimethoprim, sulfamethoxazole, and ampicillin).[6] Outbreaks of infections with these strains occurred in India,[35,36] Pakistan,[37,38] Bangladesh,[39] Vietnam,[40] the Middle East,[41] and Africa[42] (Fig. 2). These multidrug-resistant strains also carried the 100,000-to-120,000-kD *Inc*HI plasmids that encoded the resistance genes. Spread results from the clonal dissemination of individual multidrug-resistant *S. enterica* serotype typhi strains or from transfer of the plasmid to multiple *S. enterica* serotype typhi strains.[14-16] Resistance rarely emerges during the course of treatment.[43] Multidrug-resistant *S. enterica* serotype typhi are still common in many areas of Asia, although in some areas strains that are fully susceptible to all first-line antibiotics have reemerged.[44]

There have been sporadic reports of high-level resistance to ceftriaxone (minimal inhibitory concentration [MIC], 64 mg per liter) in *S. enterica* serotype typhi and *S. enterica* serotype paratyphi A,[45,46] although these strains are very rare. *S. enterica* serotype typhi strains with reduced susceptibility to fluoroquinolones have become a major problem in Asia.[47-50] An outbreak of typhoid with such strains in Tajikistan in

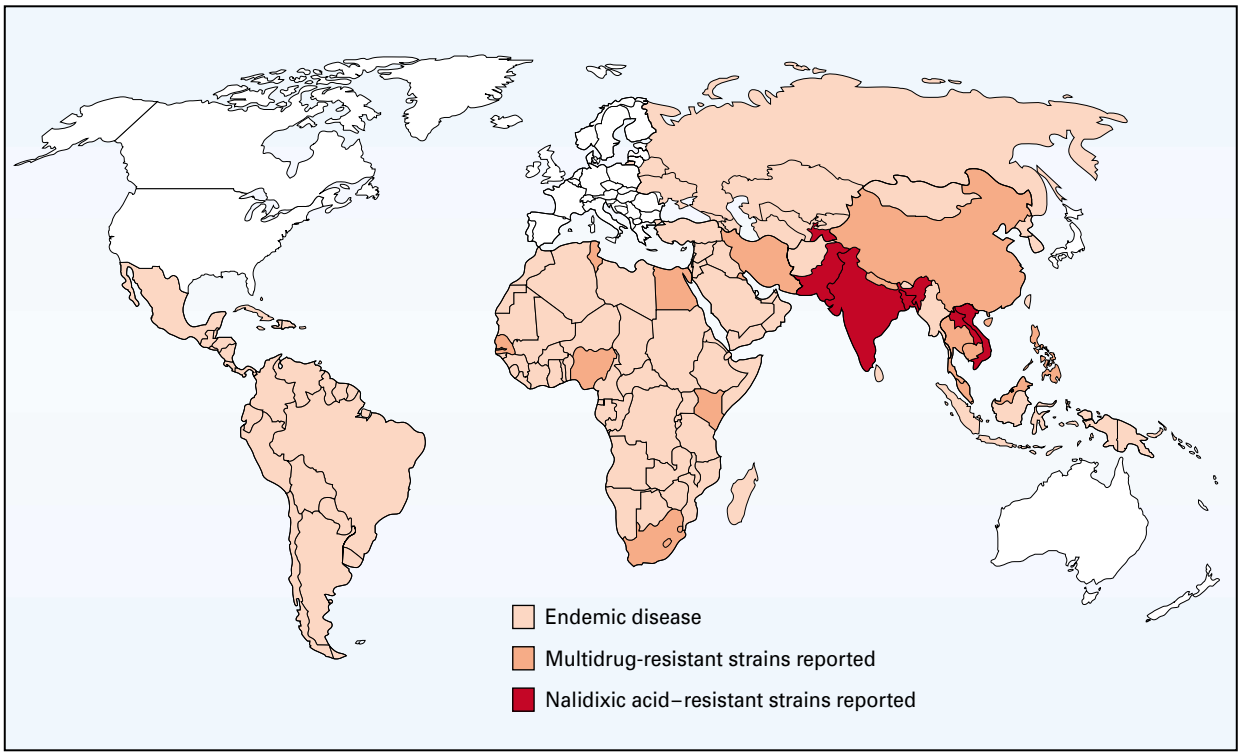

Figure 2. Global Distribution of Resistance to *Salmonella enterica* Serotype Typhi, 1990 through 2002. All shaded areas are areas of endemic disease.

1997 sickened 8000 people in a six-month period and caused 150 deaths.[10] Although they were reported to be susceptible to fluoroquinolones, by disk testing with the use of recommended break points, these organisms were resistant to nalidixic acid and the MIC of fluoroquinolones for these strains was 10 times that for fully susceptible strains. This reduction in susceptibility results in a poor clinical response to treatment.[48,49] Quinolone resistance is frequently mediated by single point mutations in the quinolone-resistance–determining region of the *gyr*A gene, characteristically occurring at position 83 of the DNA gyrase enzyme (changing serine to phenylalanine) and position 87 (changing aspartate to tyrosine or glycine).[47,48]

Quinolones, such as nalidixic acid, are a group of synthetic compounds based on the 4-quinolone nucleus. The introduction of fluorine at position 6 of the nucleus creates the fluoroquinolone group of compounds, which have substantially greater antimicrobial activity. In other Enterobacteriaciae, higher levels of quinolone resistance have been associated with additional mutations in the *gyr*A gene, mutations in other topoisomerase genes, or alterations in fluoroquinolone uptake. No such mutations have been reported yet in *S. enterica* serotype typhi, although there are sporadic reports of fully fluoroquinolone-resistant isolates.[51] Because the clinical response to fluoroquinolones in patients infected with nalidixic acid–resistant strains is greatly inferior to the response in those infected with nalidixic acid–susceptible strains, we believe that the break points for the classification of *S. enterica* serotype typhi strains according to their susceptibility to fluoroquinolones should be changed.[50] A pragmatic solution would be to classify strains that are resistant to nalidixic acid but susceptible to fluoroquinolones according to current disk-testing criteria as resistant to quinolones or nonsusceptible to fluoroquinolones. All strains that have intermediate susceptibility or resistance to fluoroquinolones on disk testing (as defined by national guidelines) should be considered fluoroquinolone-resistant.

CLINICAL FEATURES

The clinical manifestations and severity of typhoid fever vary with the patient population studied. Most patients who present to hospitals with typhoid fever are children or young adults from 5 to 25 years of age.[1,52,53] However, community-based studies in areas of endemic disease indicate that many patients with typhoid, particularly children under five years of age, may have a nonspecific illness that is not recognized clinically as typhoid.[2,3,54] Between 60 and 90 percent

of people with typhoid do not receive medical attention or are treated as outpatients.[2,3]

After a person ingests *S. enterica* serotype typhi, an asymptomatic period follows that usually lasts 7 to 14 days (range, 3 to 60). The onset of bacteremia is marked by fever and malaise. Patients typically present to the hospital toward the end of the first week after the onset of symptoms with fever, influenza-like symptoms with chills (although rigors are rare), a dull frontal headache, malaise, anorexia, nausea, poorly localized abdominal discomfort, a dry cough, and myalgia, but with few physical signs.[1,37,52,53,55] A coated tongue, tender abdomen, hepatomegaly, and splenomegaly are common. A relative bradycardia is considered common in typhoid, although in many geographic areas this has not been a consistent feature. Adults often have constipation, but in young children and in adults with HIV infection, diarrhea is more common.[31,56] It is unusual for a patient hospitalized with typhoid to have no abdominal symptoms and normal bowel movements. Initially the fever is low grade, but it rises progressively, and by the second week it is often high and sustained (39° to 40°C). A few rose spots, blanching erythematous maculopapular lesions approximately 2 to 4 mm in diameter, are reported in 5 to 30 percent of cases. They usually occur on the abdomen and chest and more rarely on the back, arms, and legs. These lesions are easily missed in dark-skinned patients.

There may be a history of intermittent confusion, and many patients have a characteristic apathetic affect. Convulsions may occur in children under five years of age.[55] The hemoglobin level, white-cell count, and platelet count are usually normal or reduced. Disseminated intravascular coagulation may be revealed by laboratory tests, but it is very rarely of clinical significance. The levels of liver enzymes are usually two to three times the upper limit of normal.

Complications occur in 10 to 15 percent of patients and are particularly likely in patients who have been ill for more than two weeks. Many complications have been described (Table 1), of which gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy are the most important. Gastrointestinal bleeding is the most common, occurring in up to 10 percent of patients. It results from erosion of a necrotic Peyer's patch through the wall of an enteric vessel. In the majority of cases, the bleeding is slight and resolves without the need for blood transfusion, but in 2 percent of cases, bleeding is clinically significant and can be rapidly fatal if a large vessel is involved. Intestinal (usually ileal) perforation is the most serious complication, occurring in 1 to 3 percent of hospitalized patients.[57,58] Perforation may be manifested by an acute abdomen or, more covertly, by simple worsening of abdominal pain, rising pulse, and falling blood pressure in an already sick patient. A reduced level of consciousness or encephalopathy, often accompanied by shock, is associated with high mortality.[59-61] The patient is commonly apathetic although rousable. Patients can be severely agitated, delirious, or obtunded, but complete stupor or coma is infrequent. The incidence of these neuropsychiatric presentations varies among countries. It ranges from 10 to 40 percent among hospitalized patients with typhoid in Indonesia[59,60] and Papua New Guinea[61] but is less than 2 percent in Pakistan[37] and Vietnam.[40] This geographic variation is unexplained. Typhoid fever during pregnancy may be complicated by miscarriage, although antimicrobial treatment has made this outcome less common.[62] Vertical intrauterine transmission from an infected mother may lead to neonatal typhoid, a rare but severe and life-threatening illness.[63]

Relapse occurs in 5 to 10 percent of patients, usually two to three weeks after the resolution of fever. The relapse is usually milder than the original attack, and the *S. enterica* serotype typhi isolate from a patient in relapse usually has the same antibiotic-susceptibility pattern as the isolate obtained from the patient during the original episode. Reinfection may also occur and can be distinguished from relapse by molecular typing.[39,64] Up to 10 percent of convalescing patients with untreated typhoid excrete *S. enterica* serotype typhi in the feces for up to three months; 1 to 4 per-

Table 1. Important Complications of Typhoid Fever.

Abdominal
Gastrointestinal perforation
Gastrointestinal hemorrhage
Hepatitis
Cholecystitis (usually subclinical)
Cardiovascular
Asymptomatic electrocardiographic changes
Myocarditis
Shock
Neuropsychiatric
Encephalopathy
Delirium
Psychotic states
Meningitis
Impairment of coordination
Respiratory
Bronchitis
Pneumonia (*Salmonella enterica* serotype typhi, *Streptococcus pneumoniae*)
Hematologic
Anemia
Disseminated intravascular coagulation (usually subclinical)
Other
Focal abscess
Pharyngitis
Miscarriage
Relapse
Chronic carriage

cent become long-term carriers, excreting the organism for more than one year. Up to 25 percent of long-term carriers have no history of typhoid. Chronic carriage is more common among women and the elderly and in patients with cholelithiasis.[65] Most carriers are asymptomatic. Patients with an abnormal urinary tract, such as those who have schistosomiasis, may excrete the organism in the urine for long periods.

The average case fatality rate is less than 1 percent, but the rate varies considerably among different regions of the world. Among hospitalized patients, the case fatality rate varies from less than 2 percent in Pakistan[37] and Vietnam[40] to 30 to 50 percent in some areas of Papua New Guinea[61] and Indonesia.[59,60] The case fatality rates are highest among children under one year of age and among the elderly.[37,52,55] However, the most important contributor to a poor outcome is probably a delay in instituting effective antibiotic treatment.

MANAGEMENT

Diagnosis

The absence of specific symptoms or signs makes the clinical diagnosis of typhoid difficult. In areas of endemic disease, a fever without evident cause that lasts more than one week should be considered typhoid until proved otherwise. Blood cultures are the standard diagnostic method; provided a large volume of blood is cultured (15 ml in adults), they are positive in 60 to 80 percent of patients with typhoid. Culture of bone marrow is more sensitive. The result is positive in 80 to 95 percent of patients with typhoid, even patients who have been taking antibiotics for several days, regardless of the duration of illness.[26,66-68] Blood cultures are less sensitive than bone marrow cultures because of the lower numbers of microorganisms in blood as compared with bone marrow.[25,26] The sensitivity of blood culture is higher in the first week of the illness, is reduced by prior use of antibiotics, and increases with the volume of blood cultured and the ratio of blood to broth. Cultures have also been made from the buffy coat of blood,[69] streptokinase-treated blood clots,[68] intestinal secretions (with the use of a duodenal string capsule),[67] and skin snips of rose spots.[66] The sensitivity of stool culture depends on the amount of feces cultured, and the positivity rate increases with the duration of the illness. Stool cultures are positive in 30 percent of patients with acute typhoid fever. For the detection of carriers, several samples should be examined because of the irregular nature of shedding.

The role of Widal's test is controversial, because the sensitivity, specificity, and predictive values of this widely used test vary considerably among geographic areas. The test detects agglutinating antibodies to the O and H antigens of *S. enterica* serotype typhi. Unfortunately, *S. enterica* serotype typhi shares these antigens with other salmonella serotypes and shares cross-reacting epitopes with other Enterobacteriaceae. Furthermore, patients with typhoid may mount no detectable antibody response or have no demonstrable rise in antibody titer. Despite this, some centers have found Widal's test helpful when it is used with locally determined cutoff points.[70,71] A Vi agglutination reaction has been used to screen for *S. enterica* serotype typhi carriers. Its reported sensitivity is 70 to 80 percent, with a specificity of 80 to 95 percent.[72] Newer serologic tests are being developed but do not yet perform well enough to ensure their widespread adoption.[73,74] DNA probes and polymerase-chain-reaction protocols have been developed to detect *S. enterica* serotype typhi directly in the blood.[75] The methods are not yet widely used and are impractical in many areas where typhoid is common.

Typhoid must be distinguished from other endemic acute and subacute febrile illnesses. Malaria, deep abscesses, tuberculosis, amebic liver abscess, encephalitis, influenza, dengue, leptospirosis, infectious mononucleosis, endocarditis, brucellosis, typhus, visceral leishmaniasis, toxoplasmosis, lymphoproliferative disease, and connective-tissue diseases should be considered. For patients in countries where typhoid is not endemic, a travel history is crucial. Clinical algorithms have been developed but have not generally been validated.

Treatment

In areas of endemic disease, more than 60 to 90 percent of cases of typhoid fever are managed at home with antibiotics and bed rest. For hospitalized patients, effective antibiotics, good nursing care, adequate nutrition, careful attention to fluid and electrolyte balance, and prompt recognition and treatment of complications are necessary to avert death.

There is strong evidence that the fluoroquinolones are the most effective drugs for the treatment of typhoid fever. In randomized, controlled trials involving patients infected by quinolone-susceptible *S. enterica* serotype typhi, these drugs have proved safe in all age groups and are rapidly effective even with short courses of treatment (three to seven days).[76-80] The average fever-clearance time is less than four days, and the cure rates exceed 96 percent. Less than 2 percent of treated patients have persistent fecal carriage or relapse (Table 2). The published data also suggest that the fluoroquinolones are more rapidly effective and are associated with lower rates of stool carriage than the traditional first-line drugs (chloramphenicol and trimethoprim–sulfamethoxazole).[76,77]

Concern has been expressed about three main issues regarding the use of fluoroquinolones in the treatment of typhoid fever: the potential for toxic effects in children, the cost, and the potential emergence of resist-

TABLE 2. POOLED DATA FROM RANDOMIZED, CONTROLLED TRIALS OF TREATMENT OF TYPHOID FEVER.*

DRUG	NO. OF TRIALS	TOTAL NO. OF PATIENTS	CHILDREN	MULTIDRUG RESISTANCE†	NALIDIXIC ACID–RESISTANCE‡	CLINICAL FAILURE§	MICROBIOLOGIC FAILURE¶	MEAN FEVER-CLEARANCE TIME	RELAPSE RATE‖	FECAL CARRIAGE**
				percent		% (95% CI)		days (95% CI)	% (95% CI)	
Chloramphenicol	35	1078	29	0	0	4.8 (3.7–6.3)	0.8 (0.3–1.6)	5.4 (5.3–5.5)	5.6 (4.3–7.2)	5.9 (4.3–7.9)
Trimethoprim–sulfamethoxazole	10	291	16	0	0	9.3 (6.3–13.4)	0 (0–1.9)	6.0 (5.8–6.2)	1.7 (0.5–4.6)	3.5 (0.9–10.6)
Ampicillin or amoxicillin	8	279	47	0	0	7.9 (5.1–11.9)	1.2 (0.3–3.8)	6.4 (6.3–6.6)	2.2 (0.9–5.0)	4.1 (2.0–7.8)
Ceftriaxone	13	393	60	41	0	8.7 (6.1–12.0)	1.5 (0.6–3.5)	6.1 (5.9–6.3)	5.3 (3.7–8.2)	1.2 (0.4–3.2)
Cefixime	4	160	100	90	0	9.4 (5.5–15.3)	1.9 (0.5–5.8)	6.9 (6.7–7.2)	3.1 (1.2–7.5)	0.8 (0.04–5.3)
Fluoroquinolone††	17	1049	25	56	4	2.1 (1.4–3.2)	0.4 (0.1–1.0)	3.9 (3.8–3.9)	1.2 (0.7–2.2)	1.5 (0.9–2.5)
Azithromycin	4	156	21	32	16	3.2 (1.2–7.7)	1.3 (0.2–5.0)	4.4 (4.2–4.5)	0 (0–3.0)	0 (0–3.0)
Aztreonam	4	101	63	31	0	6.9 (3.1–14.2)	0 (0–4.6)	5.8 (5.7–5.9)	1.0 (0.05–6.2)	1.0 (0.05–6.2)

*The data in this table were compiled from a review of 57 randomized, controlled trials performed in adults and children with typhoid fever between 1964 and 2000. The research for trials was conducted by using Medline and by searching the reference lists of articles about typhoid. The full list of papers from which these data were derived is available as Supplementary Appendix 1 with the full text of this article at http://www.nejm.org. CI denotes confidence interval.

†Multidrug-resistant strains were resistant to chloramphenicol, ampicillin, and trimethoprim–sulfamethoxazole.

‡The percentages are based on the number of trials in which susceptibility to nalidixic acid was tested.

§Clinical failure was defined as the presence of persistent symptoms or the development of complications necessitating further antimicrobial treatment.

¶Microbiologic failure was defined as a positive blood or bone marrow culture at the end of treatment.

‖A relapse was defined as the recurrence of symptoms with a positive blood or bone marrow culture after hospital discharge.

**Fecal carriage was defined as a positive fecal culture at the end of treatment.

††The fluoroquinolones tested were ciprofloxacin, ofloxacin, fleroxacin, and pefloxacin.

ance. In preclinical testing, the fluoroquinolones damaged the articular cartilage of young beagles. There is now a considerable body of reassuring evidence from the long-term use of fluoroquinolones in children with cystic fibrosis and from the short-term use of fluoroquinolones to treat typhoid fever and of fluoroquinolones or nalidixic acid to treat bacillary dysentery in children.[81-84] There has been no evidence of bone or joint toxicity, tendon rupture, or, in long-term follow-up, impairment of growth. The production of generic fluoroquinolones in Asia has reduced the price considerably. However, the emergence of quinolone resistance in areas where these drugs are inexpensive and readily available is likely to be the greatest limitation on their use. Fortunately, full fluoroquinolone resistance is still rare.

In areas where quinolone-resistant strains are uncommon, the fluoroquinolones are the current treatment of choice for all age groups (Table 3). Short courses of treatment (three to five days) are particularly useful to contain epidemics. Among patients with quinolone-resistant *S. enterica* serotype typhi infection, the rate of treatment failure is higher for those treated for less than seven days than for those treated for a longer period.[48] Treatment at the maximal recommended doses (e.g., 20 mg of ofloxacin per kilogram of body weight per day) for 7 to 10 days has been successful in 90 to 95 percent of patients with resistant infections. However, the fever-clearance times are long (seven days, on average), and the rate of fecal carriage during convalescence can be as high as 20 percent (unpublished data). Fluoroquinolones should be used at the maximal possible dose for a minimum of 10 to 14 days, and the patients should be carefully followed to determine whether they are excreting *S. enterica* serotype typhi in their feces. Unfortunately, quinolone-resistant strains are often also multidrug-resistant, and therefore the choice of drugs is limited to azithromycin or the cephalosporins, which are expensive.

The third-generation cephalosporins (ceftriaxone, cefixime, cefotaxime, and cefoperazone) and azithromycin are also effective drugs for typhoid. In randomized, controlled trials of third-generation cephalosporins, principally ceftriaxone and cefixime, the fever-clearance times averaged one week and the rates of treatment failure were 5 to 10 percent.[77,78,85,86] The relapse rates were 3 to 6 percent, and the fecal-carriage rates were less than 3 percent. Cure rates of 95 percent were achieved with five to seven days of treatment with azithromycin.[79,80,86,87] Fever resolved in four to six days, and the rates of relapse and convalescent fecal carriage were less than 3 percent. Aztreonam and imipenem are potential third-line drugs.[76,88]

Chloramphenicol, amoxicillin, and trimethoprim–sulfamethoxazole remain appropriate for the treatment of typhoid fever in areas of the world where the bacterium is still fully susceptible to these drugs and where the fluoroquinolones are not available or affordable.[89] These drugs are inexpensive, widely available, and rarely associated with side effects. They produce relief of symptoms, with defervescence usually occurring within five to seven days; however, two to three weeks of treatment is required, and adherence to a four-times-daily regimen over this period may be low. An adult will often have to take more than 250 capsules of chloramphenicol during a course of treatment. Although the cure rate is approximately 95 percent, the relapse rate is 1 to 7 percent, and the rate of convalescent excretion is 2 to 10 percent.

There are few data on the treatment of pregnant women with typhoid. The beta-lactam antibiotics are considered safe.[62] In addition, there have been several case reports of the successful use of fluoroquinolones.[90] Although these drugs have generally been avoided because of concern about safety, the general consensus is that they are also safe.[91]

Most of the data from randomized, controlled trials come from patients treated in regions where disease is endemic. There are few data from such trials of treatment in patients living in regions where the disease is not endemic or in returning travelers. Knowledge of the antibiotic susceptibility of the infecting strain is crucial in determining which drug to use. If no culture is available, knowledge of the likely susceptibility from the available global data may be useful (Fig. 2).

Severe Typhoid

The parenteral fluoroquinolones are probably the antibiotics of choice for severe infections, but there have been no randomized trials of such treatment.[92] In severe typhoid, the fluoroquinolones are given for a minimum of 10 days (Table 4). Adults and children with severe typhoid characterized by delirium, obtundation, stupor, coma, or shock benefit from the prompt administration of dexamethasone. The mortality rate was reduced from over 50 percent to 10 percent in Indonesian adults and children who were given dexamethasone at an initial dose of 3 mg per kilogram by slow intravenous infusion over a period of 30 minutes, followed by 1 mg of dexamethasone per kilogram given at the same rate every 6 hours for eight additional doses. Hydrocortisone at a lower dose was not effective.[59-61]

Patients with gastrointestinal perforation during typhoid require resuscitation with fluids, blood, and oxygen, as appropriate, followed by surgery.[57,58] At operation, the ileum, cecum, and proximal large bowel should be examined for perforations (Fig. 3). Several procedures can be performed, including intestinal resection and primary anastomosis or wedge resection or débridement of the ulcer, with primary closure of

TABLE 3. TREATMENT OF UNCOMPLICATED TYPHOID.

SUSCEPTIBILITY	FIRST-LINE ORAL DRUG			SECOND-LINE ORAL DRUG		
	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS
Fully susceptible	Fluoroquinolone (e.g., ofloxacin)*	15	5–7†	Chloramphenicol	50–75	14–21
				Amoxicillin	75–100	14
				Trimethoprim–sulfamethoxazole	8 (trimethoprim)–40 (sulfamethoxazole)	14
Multidrug-resistant	Fluoroquinolone	15	5–7	Azithromycin	8–10	7
				Third-generation cephalosporin, e.g., cefixime	20	7–14
Quinolone-resistant‡	Azithromycin or fluoroquinolone	8–10 20	7 10–14	Third-generation cephalosporin, e.g., cefixime	20	7–14

*The widely available fluoroquinolones (ofloxacin, ciprofloxacin, and pefloxacin) are all highly active and equivalent in efficacy. Norfloxacin has inadequate oral bioavailability and should not be used to treat typhoid fever.

†Three-day courses are also effective, particularly for the containment of epidemics.

‡The optimal treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, or a third-generation cephalosporin, or a 10-to-14-day course of high doses of a fluoroquinolone is effective. Combinations of these treatments are now being evaluated.

TABLE 4. TREATMENT OF SEVERE TYPHOID.

SUSCEPTIBILITY	FIRST-LINE PARENTERAL DRUG			SECOND-LINE PARENTERAL DRUG		
	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS
Fully susceptible	Fluoroquinolone (e.g., ofloxacin)*	15	10–14	Chloramphenicol	100	14–21
				Ampicillin	100	10–14
				Trimethoprim–sulfamethoxazole	8 (trimethoprim)–40 (sulfamethoxazole)	10–14
Multidrug-resistant	Fluoroquinolone	15	10–14	Ceftriaxone or cefotaxime	60 80	10–14
Quinolone-resistant	Ceftriaxone or cefotaxime	60 80	10–14	Fluoroquinolone	20	10–14

*The widely available fluoroquinolones (ofloxacin, ciprofloxacin, and pefloxacin) are all highly active and equivalent in efficacy.

the perforation. A temporary ileostomy or ileocolostomy is sometimes required. The sites of impending perforation can be sutured with serosa-to-serosa approximation. Lavage of the peritoneal cavity should be followed by closure, with or without drainage. Patients require additional parenteral antibiotics to eliminate enteric aerobes and anaerobes that may contaminate the peritoneal cavity. Early intervention is crucial, and mortality rates increase as the delay between perforation and surgery lengthens. The mortality rate after perforation varies between 10 and 32 percent.[57,58] Many cases of intestinal hemorrhage are not severe and can be managed without transfusion, but blood should be cross-matched immediately and the surgical team alerted.

Relapses should be treated in the same way as initial infections. The majority of intestinal carriers can be cured by a prolonged course of antibiotics, provided they do not have gallstones. Cure rates of approximately 80 percent have been achieved with 100 mg of ampicillin or amoxicillin per kilogram per day, taken orally, with 30 mg of probenecid per kilogram per day for 3 months; two tablets of trimethoprim–sulfamethoxazole twice daily for 3 months; or 750 mg of ciprofloxacin twice daily for 28 days; the cure rate varies with the susceptibility of the organism.[76,93] In

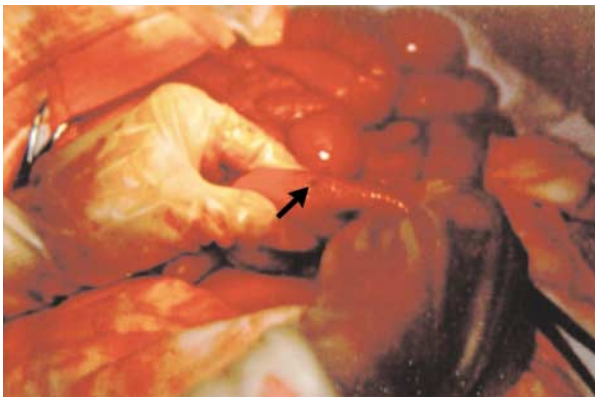

Figure 3. Gastrointestinal Perforation.
Gastrointestinal perforation (arrow), usually of the terminal ileum or proximal large bowel, is one of the most serious complications of typhoid fever.

the presence of cholelithiasis, antibiotic therapy as well as cholecystectomy may be required. In patients with chronic urinary carriage resulting from infection with *Schistosoma haematobium,* the schistosomiasis should be treated with praziquantel before the *S. enterica* serotype typhi infection.

CONTROL OF TYPHOID

In developing countries, reducing the number of cases in the general population requires the provision of safe drinking water, effective sewage disposal, and hygienic food preparation.[4] Mass immunization has been used successfully in some areas.[94] In developed countries, identification of chronic carriers is now less important than formerly. Most cases are the result of travel to areas of endemic disease. Travelers in such areas need to take particular care with food and water. Water for drinking should be boiled or bottled, food should be thoroughly cooked, and ice cream should be regarded with suspicion. Fresh vegetables or fruits that have been washed in local water are potential sources of infection.

The first parenteral whole-cell typhoid vaccine was introduced in 1896. Its efficacy was established in field trials in the 1960s in Poland, Yugoslavia, Guyana, and the Soviet Union.[95] The various vaccines offered 51 to 88 percent protection to children and young adults, lasting for up to 12 years. The chief disadvantages of the whole-cell vaccine are local discomfort and swelling and the systemic side effects that occur in 25 to 50 percent of recipients.[95]

Field studies of Ty21a, a live, attenuated oral vaccine, have shown variable protective efficacy, ranging from 96 percent after 3 years in Egypt[96] to 67 percent after 5 years in Chile[97] and 42 to 53 percent, depending on the formulation, after 2.5 years in Indonesia.[98] The vaccine is given as one capsule on days 1, 3, 5, and 7 and is suitable for adults and children over six years of age. A booster dose is recommended every five years. The vaccine is well tolerated, but because it is a live, attenuated vaccine, it should not be given to immunocompromised patients or patients taking antibiotics. Alternative oral vaccines are at different stages of development.

The parenteral Vi-based vaccine is suitable for adults and children over the age of two years and has no serious side effects. A single dose of 0.5 ml (25 μg) is administered intramuscularly. Booster doses are recommended every two years. A single injection of the Vi vaccine provided a protective efficacy of 72 percent after 17 months in Nepal[99] and 64 percent after 21 months in South Africa.[100] A new modified Vi vaccine conjugated to a nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) was evaluated recently in Vietnam. In an area where the incidence of typhoid in children two to five years of age was 414 cases per 100,000 per year, the protective efficacy was 91.5 percent.[101] An important advantage of this vaccine is that it has the potential to be immunogenic in infants under the age of two. There is no currently licensed vaccine against *S. enterica* serotype paratyphi A.

The Ty21a and Vi vaccines are recommended for travelers to areas where typhoid is endemic, household contacts of typhoid carriers, and laboratory workers likely to handle *S. enterica* serotype typhi,[4] although there is no evidence from controlled trials that these vaccines are effective outside areas of endemic disease. In areas where epidemic risk is high, mass immunization should be considered during disasters or in refugee camps, in combination with adequate provision of safe water and food.[102]

THE FUTURE

The ideal components of effective case management of typhoid fever in areas of endemic disease would be a reliable and inexpensive diagnostic test and cheap, effective oral antibiotics. The lack of a simple diagnostic test — or, indeed, of any diagnostic facilities in many areas of endemic disease — means that typhoid is a disease whose importance is underestimated worldwide. Cheap, effective oral antibiotics have been available for the past 40 to 50 years, but this situation is changing. The widespread emergence of multidrug-resistant typhoid in Africa will add an additional burden to an already overstretched health care system. The resources to pay for fluoroquinolones or cephalosporins to treat resistant cases of typhoid in this region are scarce. The threat of the emergence of resistance to the remaining drugs used to treat typhoid is also very real. There are already sporadic reports of resistance to fluoroquinolones and third-generation cephalosporins.[45,46,51] What could we recommend for

the emergency treatment of a large outbreak caused by a multidrug and fully fluoroquinolone-resistant strain?

Strategies to avert this possibility need to be considered seriously. Improvements in the provision of clean water and sanitation are critical to reduce the overall burden of typhoid, but such improvements will be slow. The use of combination chemotherapy, the evaluation of new drugs, and the wider use of vaccination in areas of endemic disease are options. In Thailand, the incidence of typhoid was reduced dramatically by a program of yearly vaccination of schoolchildren with the old whole-cell vaccine.[94] The emergence of antimicrobial resistance may change the balance of cost effectiveness for mass-vaccination programs in such areas, however. A typhoid-vaccination program for schoolchildren or, with the advent of the new conjugate Vi vaccine, as part of the Expanded Program of Immunization, should be considered.

Supported by grants from the Wellcome Trust. Dr. White is a Wellcome Trust Principal Fellow, and Dr. Farrar is a Wellcome Trust Senior Clinical Fellow.

REFERENCES

1. Osler W. The principles and practice of medicine: designed for the use of practitioners and students of medicine. 8th ed. New York: D. Appleton, 1912:1-46.
2. Lin FY, Ho VA, Bay PV, et al. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. Am J Trop Med Hyg 2000;62:644-8.
3. Sinha A, Sazawal S, Kumar R, et al. Typhoid fever in children aged less than 5 years. Lancet 1999;354:734-7.
4. Ivanoff B. Typhoid fever: global situation and WHO recommendations. Southeast Asian J Trop Med Public Health 1995;26:Suppl 2:1-6.
5. Woodward TE, Smadel JE, Ley HL Jr, Green R, Mankikar DS. Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever. Ann Intern Med 1948;29:131-4.
6. Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid: a global problem. J Med Microbiol 1996;44:317-9.
7. Ackers ML, Puhr ND, Tauxe RV, Mintz ED. Laboratory-based surveillance of *Salmonella* serotype Typhi infections in the United States: antimicrobial resistance on the rise. JAMA 2000;283:2668-73.
8. Black RE, Cisneros L, Levine MM, Banfi A, Lobos H, Rodriguez H. Case-control study to identify risk factors for paediatric endemic typhoid fever in Santiago, Chile. Bull World Health Organ 1985;63:899-904.
9. Luby SP, Faizan MK, Fisher-Hoch SP, et al. Risk factors for typhoid fever in an endemic setting, Karachi, Pakistan. Epidemiol Infect 1998;120:129-38.
10. Mermin JH, Villar R, Carpenter J, et al. A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. J Infect Dis 1999;179:1416-22.
11. Luxemburger C, Chau MC, Mai NL, et al. Risk factors for typhoid fever in the Mekong Delta, southern Viet Nam: a case-control study. Trans R Soc Trop Med Hyg 2001;95:19-23.
12. Gasem MH, Dolmans WM, Keuter MM, Djokomoeljanto RR. Poor food hygiene and housing as risk factors for typhoid fever in Semarang, Indonesia. Trop Med Int Health 2001;6:484-90.
13. Grossman DA, Witham ND, Burr DH, et al. Flagellar serotypes of *Salmonella typhi* in Indonesia: relationship among motility, invasiveness, and clinical illness. J Infect Dis 1995;171:212-6.
14. Thong K-L, Bhutta ZA, Pang T. Multidrug-resistant strains of *Salmonella enterica* serotype typhi are genetically homogenous and coexist with antibiotic-sensitive strains as distinct, independent clones. Int J Infect Dis 2000;4:194-7.
15. Connerton P, Wain J, Hien TT, et al. Epidemic typhoid in Vietnam: molecular typing of multiple-antibiotic-resistant *Salmonella enterica* serotype typhi from four outbreaks. J Clin Microbiol 2000;38:895-7.
16. Mirza S, Kariuki S, Mamun KZ, Beeching NJ, Hart CA. Analysis of plasmid and chromosomal DNA of multidrug-resistant *Salmonella enterica* serovar typhi from Asia. J Clin Microbiol 2000;38:1449-52.
17. Parkhill J, Dougan G, James KD, et al. Complete genome sequence of a multiple drug resistant *Salmonella enterica* serovar typhi CT18. Nature 2001;413:848-52.
18. McClelland M, Sanderson KE, Spieth J, et al. The complete genome sequence of *Salmonella enterica* serovar typhimurium LT2. Nature 2001; 413:852-6.
19. Blattner FR, Plunkett G III, Bloch CA, et al. The complete genome sequence of *Escherichia coli* K-12. Science 1997;277:1453-74.
20. Sherburne CK, Lawley TD, Gilmour MW, et al. The complete DNA sequence and analysis of R27, a large IncHI plasmid from *Salmonella typhi* that is temperature sensitive for transfer. Nucleic Acids Res 2000;28:2177-86.
21. Taylor DE, Chumpitaz JC, Goldstein F. Variability of IncHI1 plasmids from *Salmonella typhi* with special reference to Peruvian plasmids encoding resistance to trimethoprim and other antibiotics. Antimicrob Agents Chemother 1985;28:452-5.
22. Hornick RB, Greisman SE, Woodward TE, DuPont HL, Dawkins AT, Snyder MJ. Typhoid fever: pathogenesis and immunologic control. N Engl J Med 1970;283:686-91, 739-46.
23. House D, Bishop A, Parry CM, Dougan G, Wain J. Typhoid fever: pathogenesis and disease. Curr Opin Infect Dis 2001;14:573-8.
24. Butler T, Bell WR, Levin J, Linh NN, Arnold K. Typhoid fever: studies of coagulation, bacteremia, and endotoxemia. Arch Intern Med 1978; 138:407-10.
25. Wain J, Diep TS, Ho VA, et al. Quantitation of bacteria in blood of typhoid fever patients and relationship between counts and clinical features, transmissibility, and antibiotic resistance. J Clin Microbiol 1998;36:1683-7.
26. Wain J, Bay VB, Ha V, et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. J Clin Microbiol 2001;39:1571-6.
27. Butler T, Ho M, Acharya G, Tiwari M, Gallati H. Interleukin-6, gamma interferon, and tumour necrosis factor receptors in typhoid fever related to outcome of antimicrobial therapy. Antimicrob Agents Chemother 1993; 37:2418-21.
28. Keuter M, Dharmana E, Gasem MH, et al. Patterns of proinflammatory cytokines and inhibitors during typhoid fever. J Infect Dis 1994;169: 1306-11.
29. Bhutta ZA, Mansoorali N, Hussain R. Plasma cytokines in pediatric typhoidal salmonellosis: correlation with clinical course and outcome. J Infect 1997;35:253-6.
30. Everest P, Wain J, Roberts M, Rook G, Dougan G. The molecular mechanisms of severe typhoid fever. Trends Microbiol 2001;9:316-20.
31. Gotuzzo E, Frisancho O, Sanchez J, et al. Association between the acquired immunodeficiency syndrome and infection with Salmonella typhi or Salmonella paratyphi in an endemic typhoid area. Arch Intern Med 1991; 151:381-2.
32. Crewe-Brown HH, Kartaedt AS, Saunders GL, Khoosal M, McCarthy K. Invasive *Salmonella* species and HIV infection. In: Proceedings of the 12th World AIDS Conference, Geneva, June 28–July 3, 1998:284. abstract.
33. Dunstan SJ, Stephens HA, Blackwell JM, et al. Genes of the class II and class III major histocompatibility complex are associated with typhoid fever in Vietnam. J Infect Dis 2001;183:261-8.
34. Dunstan SJ, Ho VA, Duc CM, et al. Typhoid fever and genetic polymorphisms at the natural resistance-associated macrophage protein 1. J Infect Dis 2001;183:1156-60.
35. Threlfall EJ, Ward LR, Rowe B, et al. Widespread occurrence of multiple drug-resistant *Salmonella typhi* in India. Eur J Clin Microbiol Infect Dis 1992;11:990-3.
36. Shanahan PM, Jesudason MV, Thomson CJ, Amyes SG. Molecular analysis of and identification of antibiotic resistance genes in clinical isolates of *Salmonella typhi* from India. J Clin Microbiol 1998;36:1595-600.
37. Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. Arch Dis Child 1996;75:214-7.
38. Shanahan PM, Karamat KA, Thomson CJ, Amyes SGB. Characterization of multi-drug resistant *Salmonella typhi* from Pakistan. Epidemiol Infect 2000;124:9-16.
39. Hermans PWM, Saha SK, van Leeuwen WJ, Verbrugh HA, van Belkum A, Goessens WHF. Molecular typing of *Salmonella typhi* strains from Dhaka (Bangladesh) and development of DNA probes identifying plasmid-encoded multidrug-resistant isolates. J Clin Microbiol 1996;34:1373-9.
40. Hoa NTT, Diep TS, Wain J, et al. Community-acquired septicaemia in southern Viet Nam: the importance of multidrug-resistant *Salmonella typhi*. Trans R Soc Trop Med Hyg 1998;92:503-8.
41. Spread of multiresistant *Salmonella typhi*. Lancet 1990;336:1065-6.
42. Kariuki S, Gilks C, Revathi G, Hart CA. Genotypic analysis of multidrug-resistant *Salmonella enterica* serovar typhi, Kenya. Emerg Infect Dis 2000;6:649-51.

43. Schwalbe RS, Hoge CW, Morris JG, O'Hanlon PN, Crawford RA, Gilligan PH. *In vivo* selection for transmissible drug resistance in *Salmonella typhi* during antimicrobial therapy. Antimicrob Agents Chemother 1990;34:161-3.
44. Sood S, Kapil A, Das B, Jain Y, Kabra SK. Re-emergence of chloramphenicol-sensitive Salmonella typhi. Lancet 1999;353:1241-2.
45. Bhutta ZA, Farooqui BJ, Sturm AW. Eradication of a multiple drug resistant *Salmonella paratyphi* A causing meningitis with ciprofloxacin. J Infect 1992;25:215-9.
46. Saha SK, Talukder SY, Islam M, Saha S. A highly ceftriaxone-resistant Salmonella typhi in Bangladesh. Pediatr Infect Dis J 1999;18:387.
47. Brown JC, Shanahan PM, Jesudason MV, Thomson CJ, Amyes SG. Mutations responsible for reduced susceptibility to 4-quinolones in clinical isolates of multi-resistant *Salmonella typhi* in India. J Antimicrob Chemother 1996;37:891-900.
48. Wain J, Hoa NT, Chinh NT, et al. Quinolone-resistant *Salmonella typhi* in Viet Nam: molecular basis of resistance and clinical response to treatment. Clin Infect Dis 1997;25:1404-10.
49. Threlfall EJ, Ward LR, Skinner JA, Smith HR, Lacey S. Ciprofloxacin-resistant Salmonella typhi and treatment failure. Lancet 1999;353:1590-1.
50. Threlfall EJ, Skinner JA, Ward LR. Detection of decreased *in vitro* susceptibility to ciprofloxacin in *Salmonella enterica* serotypes typhi and paratyphi A. J Antimicrob Chemother 2001;48:740-1.
51. Mehta G, Randhawa VS, Mohapatra NP. Intermediate susceptibility to ciprofloxacin in *Salmonella typhi* strains in India. Eur J Clin Microbiol Infect Dis 2001;20:760-1.
52. Stuart BM, Pullen RL. Typhoid: clinical analysis of three hundred and sixty cases. Arch Intern Med 1946;78:629-61.
53. Huckstep RL. Typhoid fever and other salmonella infections. Edinburgh, Scotland: E.&S. Livingstone, 1962.
54. Ferreccio C, Levine MM, Manterola A, et al. Benign bacteremia caused by *Salmonella typhi* and *paratyphi* in children younger than 2 years. J Pediatr 1984;106:899-901.
55. Butler T, Islam A, Kabir I, Jones PK. Patterns of morbidity and mortality in typhoid fever dependent on age and gender: a review of 552 hospitalized patients with diarrhea. Rev Infect Dis 1991;13:85-90.
56. Vinh H, Wain J, Vo TN, et al. Two or three days of ofloxacin treatment for uncomplicated multidrug-resistant typhoid fever in children. Antimicrob Agents Chemother 1996;40:958-61.
57. Bitar RE, Tarpley J. Intestinal perforation in typhoid fever: a historical and state-of-the-art review. Rev Infect Dis 1985;7:257-71.
58. van Basten JP, Stockenbrugger R. Typhoid perforation: a review of the literature since 1960. Trop Geogr Med 1994;46:336-9.
59. Hoffman SL, Punjabi NH, Kumala S, et al. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. N Engl J Med 1984;310:82-8.
60. Punjabi NH, Hoffman SL, Edman DC, et al. Treatment of severe typhoid fever in children with high dose dexamethasone. Pediatr Infect Dis J 1988;7:598-600.
61. Rogerson SJ, Spooner VJ, Smith TA, Richens J. Hydrocortisone in chloramphenicol-treated severe typhoid fever in Papua New Guinea. Trans R Soc Trop Med Hyg 1991;85:113-6.
62. Seoud M, Saade G, Uwaydah M, Azoury R. Typhoid fever in pregnancy. Obstet Gynecol 1988;71:711-4.
63. Reed RP, Klugman KP. Neonatal typhoid fever. Pediatr Infect Dis J 1994;13:774-7.
64. Wain J, Hien TT, Connerton P, et al. Molecular typing of multiple-antibiotic-resistant *Salmonella enterica* serovar typhi from Vietnam: application to acute and relapse cases of typhoid fever. J Clin Microbiol 1999; 37:2466-72.
65. Levine MM, Black RE, Lanata C. Precise estimation of the numbers of chronic carriers of *Salmonella typhi* in Santiago, Chile, an endemic area. J Infect Dis 1982;6:724-6.
66. Gilman RH, Terminel M, Levine MM, Hernandez-Mendoza P, Hornick RB. Relative efficacy of blood, urine, rectal swab, bone marrow, and rose-spot cultures for recovery of *Salmonella typhi* in typhoid fever. Lancet 1975;1:1211-3.
67. Vallenas C, Hernandez H, Kay B, Black R, Gotuzzo E. Efficacy of bone marrow, blood, stool and duodenal contents cultures for bacteriologic confirmation of typhoid fever in children. Pediatr Infect Dis 1985;4:496-8.
68. Hoffman SL, Edman DC, Punjabi NH, et al. Bone marrow aspirate culture superior to streptokinase clot culture and 8 ml 1:10 blood-to-broth ratio blood culture for diagnosis of typhoid fever. Am J Trop Med Hyg 1986;35:836-9.
69. Rubin FA, McWhirter PD, Burr D, et al. Rapid diagnosis of typhoid fever through identification of *Salmonella typhi* within 18 hours of specimen acquisition by culture of the mononuclear cell-platelet fraction of blood. J Clin Microbiol 1990;28:825-7.
70. Clegg A, Passey M, Omena M, Karigifa KK, Suve N. Re-evaluation of the Widal agglutination test in response to the changing pattern of typhoid fever in the highlands of Papua New Guinea. Acta Trop 1994;57:255-63.
71. Parry CM, Hoa NT, Diep TS, et al. Value of a single-tube Widal test in diagnosis of typhoid fever in Vietnam. J Clin Microbiol 1999;37:2882-6.
72. Lanata CF, Levine MM, Ristori C, et al. Vi serology in detection of chronic *Salmonella typhi* carriers in an endemic area. Lancet 1983;2:441-3.
73. Bhutta ZA, Mansurali N. Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: a prospective comparative evaluation of two dot-enzyme immunoassays and the Widal test. Am J Trop Med Hyg 1999; 61:654-7.
74. House D, Wain J, Ho VA, et al. Serology of typhoid fever in an area of endemicity and its relevance to diagnosis. J Clin Microbiol 2001;39: 1002-7.
75. Song JH, Cho H, Park MY, Na DS, Moon HB, Pai CH. Detection of *Salmonella typhi* in the blood of patients with typhoid fever by polymerase chain reaction. J Clin Microbiol 1993;31:1439-43.
76. Gotuzzo E, Carrillo C. Quinolones in typhoid fever. Infect Dis Clin Pract 1994;3:345-51.
77. White NJ, Parry CM. The treatment of typhoid fever. Curr Opin Infect Dis 1996;9:298-302.
78. Cao XT, Kneen R, Nguyen TA, Truong DL, White NJ, Parry CM. A comparative study of ofloxacin and cefixime for treatment of typhoid fever in children. Pediatr Infect Dis J 1999;18:245-8.
79. Girgis NI, Butler T, Frenck RW, et al. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that includes patients with multidrug resistance. Antimicrob Agents Chemother 1999;43:1441-4.
80. Chinh NT, Parry CM, Ly NT, et al. A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant and nalidixic acid-resistant enteric fever. Antimicrob Agents Chemother 2000; 44:1855-9.
81. Schaad UB, abdus Salam M, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J 1995;14:1-9.
82. Bethell DB, Hien TT, Phi LT, et al. Effects on growth of single short courses of fluoroquinolones. Arch Dis Child 1996;74:44-6.
83. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis 1997;25:1196-204.
84. Doherty CP, Saha SK, Cutting WA. Typhoid fever, ciprofloxacin and growth in young children. Ann Trop Paediatr 2000;20:297-303.
85. Memon IA, Billoo AG, Memon HI. Cefixime: an oral option for the treatment of multidrug-resistant enteric fever in children. South Med J 1997;90:1204-7.
86. Frenck RW Jr, Nakhla I, Sultan Y, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. Clin Infect Dis 2000;31:1134-8.
87. Butler T, Sridhar CB, Daga MK, et al. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999;44:243-50.
88. Bhutta ZA. Quinolone-resistant *Salmonella paratyphi* B meningitis in a newborn: a case report. J Infect 1997;35:308-10.
89. Herzog C. Chemotherapy of typhoid fever: a review of literature. Infection 1976;4:166-73.
90. Leung D, Venkatesan P, Boswell T, Innes JA, Wood MJ. Treatment of typhoid in pregnancy. Lancet 1995;346:648.
91. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother 1998;42:1336-9.
92. Dutta P, Rasaily R, Saha MR, et al. Ciprofloxacin for treatment of severe typhoid fever in children. Antimicrob Agents Chemother 1993;37: 1197-9.
93. Ferreccio C, Morris JG Jr, Valdivieso C, et al. Efficacy of ciprofloxacin in the treatment of chronic typhoid carriers. J Infect Dis 1988;157:1235-9.
94. Bodhidatta L, Taylor DN, Thisyakorn U, Echeverria P. Control of typhoid fever in Bangkok, Thailand, by annual immunization of schoolchildren with parenteral typhoid vaccine. Rev Infect Dis 1987;9:841-5.
95. Engels EA, Falagas ME, Lau J, Bennish ML. Typhoid fever vaccines: a metaanalysis of studies on efficacy and toxicity. BMJ 1998;316:110-6.
96. Wahdan MH, Serie C, Cerisier Y, Sallam S, Germanier R. A controlled field trial of live *Salmonella typhi* strain Ty 21a oral vaccine against typhoid: three-year results. J Infect Dis 1982;145:292-5.
97. Levine MM, Ferreccio C, Black RE, Germanier R. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. Lancet 1987;1:1049-52.

98. Simanjuntak CH, Paleologo FP, Punjabi NH, et al. Oral immunisation against typhoid fever in Indonesia with Ty21a vaccine. Lancet 1991;338:1055-9.
99. Acharya IL, Lowe CU, Thapa R, et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi:* a preliminary report. N Engl J Med 1987;317:1101-4.
100. Klugman KP, Gilbertson IT, Koornhof HJ, et al. Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. Lancet 1987;2:1165-9.
101. Lin FYC, Ho VA, Khiem HB, et al. The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med 2001;344:1263-9.
102. Tarr PE, Kuppens L, Jones TC, Ivanoff B, Aparin PG, Heymann DL. Considerations regarding mass vaccination against typhoid fever as an adjunct to sanitation and public health measures: potential use in an epidemic in Tajikistan. Am J Trop Med Hyg 1999;61:163-70.