

# Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive *Salmonella* Infections

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## SUMMARY

*Salmonella enterica* infections are common causes of bloodstream infection in low-resource areas, where they may be difficult to distinguish from other febrile illnesses and may be associated with a high case fatality ratio. Microbiologic culture of blood or bone marrow remains the mainstay of laboratory diagnosis. Antimicrobial resistance has emerged in *Salmonella enterica*, initially to the traditional first-line drugs chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. Decreased fluoroquinolone susceptibility and then fluoroquinolone resistance have developed in association with chromosomal mutations in the quinolone resistance-determining region of genes encoding DNA gyrase and topoisomerase IV and also by plasmid-mediated resistance mechanisms. Resistance to extended-spectrum cephalosporins has occurred more often in nontyphoidal than in typhoidal *Salmonella* strains. Azithromycin is effective for the management of uncomplicated typhoid fever and may serve as an alternative oral drug in areas where fluoroquinolone resistance is common. In 2013, CLSI lowered the ciprofloxacin susceptibility breakpoints to account for accumulating clinical, microbiologic, and pharmacokinetic-pharmacodynamic data suggesting that revision was needed for contemporary invasive *Salmonella* infections. Newly established CLSI guidelines for azithromycin and *Salmonella enterica* serovar Typhi were published in CLSI document M100 in 2015.

## INTRODUCTION

*Salmonella enterica* is a leading cause of community-acquired bloodstream infections in many low- and middle-income countries (1, 2). *Salmonella enterica* serovars Typhi, Paratyphi A, Paratyphi B, and Paratyphi C may be referred to collectively as typhoidal *Salmonella*, whereas other serovars are grouped as nontyphoidal *Salmonella* (NTS). Typhoidal *Salmonella* strains are human host-restricted organisms that cause typhoid fever and paratyphoid fever, together referred to as enteric fever. NTS strains may be host generalists, infecting or colonizing a broad range of vertebrate animals, or may be adapted or restricted to particular nonhuman animal species (3).

We review invasive *Salmonella* infections with respect to epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management. In particular, we focus on the development of antimicrobial resistance and recent changes to the interpretation of antimicrobial susceptibility tests

for fluoroquinolones and to establishment of methods and interpretive criteria for azithromycin.

## EPIDEMIOLOGY AND CLINICAL ASPECTS

### Typhoidal *Salmonella*

**Burden of disease.** In 2000, typhoid fever was estimated to cause approximately 21.7 million illnesses and 216,000 deaths and paratyphoid fever 5.4 million illnesses (4). Typhoid and paratyphoid fevers were included in the Global Burden of Disease 2010 (GBD 2010) project, when they were together estimated to account for 12.2 million disability-adjusted life years (5) and 190,200 deaths (6). Children in south-central and southeast Asia are at particular risk (4). The International Vaccine Institute estimated that there were 11.9 million typhoid fever illnesses and 129,000 deaths in low- and middle-income countries in 2010 (Fig. 1) (7). Typhoid fever appears to have become more common in sub-Saharan African countries (8) or to have been underappreciated there in the past (9). In some Asian countries, *Salmonella* serovar Paratyphi A has accounted for a growing proportion of enteric fever (10, 11).

**Sources and modes of transmission.** Typhoidal *Salmonella* is transmitted predominantly through water or food contaminated with human feces. The risk for infection is high in low- and middle-income countries where typhoidal *Salmonella* is endemic and that have poor sanitation and lack of access to safe food and water (4). Enteric fever in high-income countries is usually acquired abroad and is associated with travel to areas of endemicity (12), although clusters may be associated with food preparers who are chronic carriers of *Salmonella* serovar Typhi (13).

**Host risk and protective factors.** A range of host risk and protective factors have been identified for typhoidal *Salmonella* infection. *Salmonella enterica* is acid susceptible and must survive the gastric acid barrier to successfully establish infection in the terminal ileum. Gastric acid secretion has been shown to be suppressed during acute enteric fever, subsequently returning to normal and with the degree of acid suppression relating to the infection severity (14, 15). The acid tolerance of the organism may be an important determinant of transition to the small intestine and can vary with the infecting serovar (16).

Past infection with *Helicobacter pylori* has been suggested to be associated with typhoid fever, perhaps because both diseases are associated with reduced gastric acidity. In a case-control study in India, the presence of serum anti-*H. pylori* immunoglobulin G antibodies was associated with typhoid fever with an adjusted

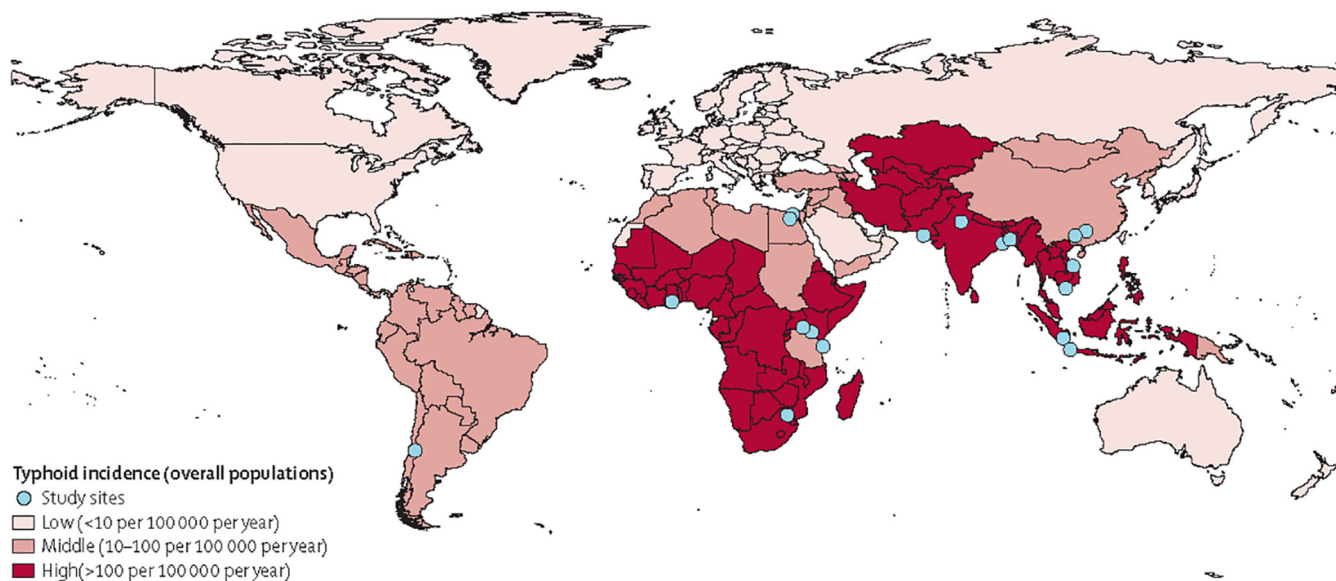


FIG 1 Typhoid incidence in low-income and middle-income countries (risk adjusted and corrected for blood culture sensitivity). (Reprinted from reference 7 with permission from Elsevier.)

odds ratio (OR) of 2.03 (95% confidence interval [CI], 1.02 to 4.01) (17). In this study, illiteracy, being part of a nuclear family, nonuse of soap, and consumption of ice cream were also associated with an increased risk of typhoid. *H. pylori* IgG antibodies develop 1 to 3 months after acute infection and so could indicate either active or previous infection. In a similar case-control study done in Jakarta, Indonesia, with an age-stratified analysis, the level of *H. pylori* IgG but not IgA antibody was higher in typhoid fever patients than in community controls (18). Furthermore, plasma gastrin levels, indicative of hypochlorhydria, were not significantly elevated in typhoid fever cases compared to controls. In a multivariable analysis, there was an association of *H. pylori* IgG seropositivity with typhoid fever with an odds ratio of 1.93 (95% CI, 1.10 to 3.40). However, the authors suggested that the association may result from common environmental exposure to poor hygiene rather than implying a causal relationship through reduced gastric acid secretion.

A limited number of studies have demonstrated host genetic factors that influence susceptibility to enteric fever. The cystic fibrosis transmembrane conductance regulator (CFTR) is a protein expressed on the gastric mucosa. *In vitro* experiments have shown that the wild-type protein facilitates adherence and entry of *Salmonella* serovar Typhi, but not *Salmonella* serovar Typhimurium, into intestinal epithelial cells (19). This binding and entry are mediated by an interaction between *Salmonella* serovar Typhi lipopolysaccharide (LPS) and type IVb pilus and CFTR protein residues (20, 21). Expression of CFTR on the intestinal epithelium is stimulated by the presence of *Salmonella* serovar Typhi and commensal bacteria in the intestine (22, 23). Mutations in CFTR, such as F508del, are associated with cystic fibrosis. In the presence of this mutation there is no uptake of *Salmonella* serovar Typhi into intestinal epithelial cells, and in heterozygotes uptake into cells is reduced (19). Thus, the F508del mutant may provide protection against infection following exposure to *Salmonella* serovar Typhi. A case-control study in Jakarta, Indonesia, of mutations in the CFTR allele and enteric fever found no participants with the

F508del mutation. It is possible that variations in CFTR other than F508del may provide protection against enteric fever. A microsatellite polymorphism in intron 8, IVS8CA, of the CFTR gene was associated with protection from enteric fever ( $P = 0.003$ ) (24). In a further analysis of additional regions, the presence of one or more protein-expressing variations, including the IVS8 TG<sub>11</sub>TG<sub>12</sub> genotype, provided a modest protection from enteric fever (OR, 0.57;  $P < 0.01$ ) (25).

Immune defense against enteric fever is likely to depend in part at least on cellular immunity. A study in Vietnam showed associations between major histocompatibility complex (MHC) class II and class III genes and enteric fever (26). Alleles of HLA-DR, HLA-DQ, and the proinflammatory gene *TNFA* were associated with either resistance or susceptibility to enteric fever among hospitalized patients. Circulating levels of both tumor necrosis factor alpha (TNF- $\alpha$ ) and soluble TNF receptor have been reported to be elevated in enteric fever and higher in severe disease (27, 28). The capacity to secrete TNF- $\alpha$  following *ex vivo* stimulation has been shown to be reduced in the acute phase of typhoid fever, with the degree correlating with severity of disease and delayed recovery (28, 29). The association with susceptibility to enteric fever and the polymorphism in the tumor necrosis factor alpha gene (*TNFA*-308) could not be replicated in an Indonesian population with community-diagnosed enteric fever, and there were no associations with polymorphisms in a number of other proinflammatory genes (30). A possible explanation for the discrepancy in the results is that the association of *TNFA* polymorphisms is with disease severity rather than susceptibility to infection. Of interest, HLA-DR haplotypes were associated with protection from severe enteric fever among Indonesian patients, although this could not be linked with TNF- $\alpha$  production capacity (31). Further analysis of the Vietnamese population again suggested that a haplotype in the *TNF* region gives protection against enteric fever, but the causative disease locus remains to be determined (32). In a recent genome-wide association study of patients in Vietnam and Nepal with blood culture-confirmed enteric fever, a strong association

was found for *HLA-DRB1* as a major contributor to resistance against enteric fever, presumably through antigen presentation (33).

Toll-like receptors (TLRs) mediate the innate immune responses to bacterial pathogens. TLR5 binds to bacterial flagellin and TLR4 to LPS. Among Vietnamese patients with enteric fever there were no significant associations with the TLR5<sup>392STOP</sup> polymorphisms (34). There were also no associations with TLR4 polymorphism. However, because of low gene frequencies, the sample may have been inadequate to give a definitive answer (35). In the mouse model of typhoid fever, control of *Salmonella* serovar Typhimurium infection is dependent on the natural resistance-associated macrophage protein 1 (Nramp1), but in Vietnamese patients with enteric fever, there was no allelic association between the *NRAMP1* alleles and typhoid fever susceptibility (36). Polymorphisms in the *PARK2/PACRG* gene cluster, linked to ubiquitination, and proteasome-mediated protein degradation previously found to be associated with susceptibility to infection with *Mycobacterium leprae* were weakly associated with susceptibility to enteric fever in an Indonesian population (37).

The relationship between HIV infection and enteric fever has not been studied in detail. In the early 1990s, Peruvian patients with HIV infection were reported to be at increased risk of *Salmonella* serovar Typhi disease (38). Subsequent reports in Africa and Asia highlighted the association of nontyphoidal *Salmonella* serovars, rather than *Salmonella* serovar Typhi, with HIV (1, 3). In a study of unselected hospitalized adults with fever in Tanzania, HIV appeared to be protective against *Salmonella* serovar Typhi infection (odds ratio, 0.12; 95% CI, 0.03 to 0.49;  $P = 0.001$ ) (39). The 26 positive *Salmonella* serovar Typhi cultures were taken from 24 (9.8%) of 244 HIV-uninfected patients and two (1.2%) of 161 HIV-infected patients. A similar inverse association between typhoid and HIV infection was noted in a meta-analysis of bloodstream infection studies from Africa (1). The use of hospitalized patients may be a source of bias, and the relationship requires further study.

**Presenting symptoms and signs.** In areas of endemicity, patients admitted to hospital are usually school-aged children or young adults between 5 and 25 years of age, and both sexes are affected equally (40–42). Many patients do not require admission to hospital, due to either mild disease, self-medication, or being treated in health stations, clinics, or as hospital outpatients (43–45). These community-managed cases may be of nonspecific illness that is not recognized clinically as enteric fever, especially among children under 5 years of age (46–48).

After ingestion of *Salmonella* serovar Typhi or Paratyphi A, an asymptomatic period follows that usually lasts 7 to 14 days (range, 3 to 60 days). Human challenge models, both in the 1950s to 1970s (49) and more recently (50), contributed to the understanding of incubation and very early symptoms in typhoid fever. These studies have shown that a higher infecting dose is associated with a higher attack rate and a shorter interval to bacteremia but has no influence on the time to symptom development or disease severity. Recent human challenge studies have also demonstrated that a proportion of patients develop a subclinical or asymptomatic bacteremia and that fecal shedding can occur in the period before symptom development, during primary infection (51). As symptomatic disease develops, the predominant symptom is the fever (40–42, 52). The temperature rises gradually during the first week of the illness and reaches a high plateau of 39 to 40°C the following



FIG 2 Rose spots on the abdomen of a patient with typhoid fever. (Reprinted from reference 603.)

week. There is little diurnal variation, although the pattern may be modified by anti-pyretic medications. Patients can have influenza-like symptoms, a dull frontal headache, malaise, anorexia, a dry cough, sore throat, and occasionally epistaxis. Constipation is a frequent early symptom although many patients will experience diarrhea at some point. Enteric fever can present as a diarrheal illness and occasionally with bloody diarrhea. Most patients have abdominal pain that is diffuse and poorly localized. Nausea is common, and vomiting occurs in more severe cases. It is unusual for a patient hospitalized with typhoid to have no abdominal symptoms and normal bowel movements. Rigors are uncommon and this can be a useful feature to distinguish the illness from malaria (53).

Besides fever, physical examination findings may be few. A slightly distended abdomen with a “doughy” consistency and diffuse tenderness is common. Occasionally the pain and tenderness is intense in the right iliac fossa, mimicking appendicitis, or may be more generalized, raising the possibility of peritonitis. Moderate soft and tender hepatomegaly and splenomegaly eventually develop in most patients. A relative bradycardia is described as being common in enteric fever, although some reports suggest that a tachycardia is more common and that a relative bradycardia, when present, is not specific for enteric fever (54–57). Rose spots, a blanching erythematous maculopapular rash with lesions approximately 2 to 4 mm in diameter, have been reported in 1 to 30% of cases (Fig. 2) (41, 58). They usually occur on the abdomen and chest and more rarely on the back, arms, and legs. Rose spots are easily missed in dark-skinned patients. Abnormal lung sounds, especially scattered wheezes, are common and can suggest pneumonia, but if the chest radiograph is normal and fever high, enteric fever should be considered. There may be a history of intermittent confusion, and many patients have a characteristic apathetic affect. Important differences in children, compared to adults, are a greater frequency of diarrhea and vomiting, jaundice, febrile convulsions, nephritis, or typhoid meningitis (59–62). Enteric fever may also complicate pregnancy and rarely cause neonatal infection (63, 64).

If the disease is untreated, by the second to fourth week patients may become increasingly sick with weight loss, weakness,

**TABLE 1** Complications of enteric fever

Complication
Gastrointestinal bleeding
Intestinal perforation (usually of terminal ileum, occasionally of colon)
Encephalopathy accompanied by hemodynamic shock
Hepatitis
Cholecystitis
Pneumonia (may be due to secondary infection with other organisms such as <i>Streptococcus pneumoniae</i> )
Myocarditis
Acute kidney injury, nephritis
Deep-seated abscess (e.g., spleen, large joint, bone)
Anemia
Meningitis (in infants)
Neurological disturbance (cerebellar ataxia)
Miscarriage
Psychiatric disturbance
Disseminated intravascular coagulation
Relapse
Chronic carriage (fecal or urinary carriage for >1 yr)
Carcinoma of gallbladder

and an altered mental state, and complications develop (40–42). Complications occur in 10 to 15% of hospitalized patients and are particularly likely in patients who have been ill for more than 2 weeks. Many complications have been described (Table 1), of which gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy are most closely associated with risk for death (65–67). Other complications of enteric fever include psychiatric disturbance and pneumonia. Paratyphoid fever has been described as a less severe infection than typhoid fever. However, recent studies suggest that *Salmonella* serovar Paratyphi A, an increasing problem in many areas in Asia (10, 11), can cause a disease with severity equal to that of *Salmonella* serovar Typhi (68).

**Patient outcomes. (i) Complications.** Gastrointestinal bleeding resulting from the erosion of a necrotic ileal Peyer's patch through the wall of an enteric vessel may develop in up to 10% of hospitalized patients (41, 69, 70). Bleeding is usually slight and self-limited, resolving without the need for blood transfusion. However, in some cases bleeding is substantial, and it can be rapidly fatal when a large vessel is involved. Evidence for silent gastrointestinal bleeding may be sudden collapse of the patient or a steadily falling hematocrit.

Intestinal perforation, usually involving the ileum but occasionally involving the colon, is a serious complication of enteric fever (41, 69–74). This may occur in 1 to 3% of hospitalized patients (41, 70, 75) and be manifest by an acute abdomen or more insidiously by worsening abdominal pain, a rising pulse, and falling blood pressure in an already-sick patient. Severely ill patients often display restlessness, hypotension, and tachycardia. A chest radiograph may show free gas under the diaphragm. Abdominal ultrasound is useful for demonstrating and aspirating feculent fluid in the peritoneal cavity.

Studies from Indonesia and Papua New Guinea have revealed an important subgroup of patients with a high case fatality ratio associated with mental confusion or shock (systolic blood pressure of <90 mm Hg in adults or <80 mm Hg in children) and with evidence of decreased skin, cerebral, or renal perfusion (76–78). The mental state of the patient may range from apathetic although rousable to severely agitated, delirious, or obtunded. Complete

stupor or coma is infrequent. Patients with advanced illness may display the “typhoid facies,” described as a thin, flushed face with a staring, apathetic expression. Mental apathy may progress to an agitated delirium, frequently accompanied by hand tremor, tremulous speech, and gait ataxia. If the patient's condition deteriorates further, the features described in the writings of Louis and Osler may occur, including muttering delirium, twitching of the fingers and wrists, agitated plucking at the bedclothes, and a staring and unrousable stupor, also known as coma vigil (40).

A wide range of other complications has been described. The most common include cholecystitis, hepatitis, pneumonia, acute kidney injury, and myocarditis (69, 70). Typhoid fever during pregnancy may be complicated by miscarriage but appears to be mitigated by antimicrobial treatment (63). Mother-to-child transmission may lead to neonatal typhoid, a rare but severe and life-threatening illness (64, 79). Meningitis occurs among children below 1 year of age (62).

In the preantimicrobial era, enteric fever carried a case fatality ratio of approximately 10 to 30% (40, 41, 80). With effective antimicrobials, the case fatality ratio is usually less than 1%. Reported case fatality ratios have varied from less than 2% in Pakistan (59) and Vietnam (66, 70) to 30 to 50% in some areas of Indonesia (76, 77) and Papua New Guinea (78). Severe and fatal disease has been associated with both male and female sex, extremes of age, and antimicrobial drug resistance (59, 65, 67, 70, 73, 81). The most important contributor to a poor outcome is probably a delay in instituting effective antimicrobial treatment.

**(ii) Relapse and reinfection.** Typhoid fever relapse is manifest by a second episode of fever, often but not always milder than the first, occurring 1 week to 3 weeks after the recovery from the first episode (52). Relapse may occur in as many as 5 to 10% of untreated or chloramphenicol-treated typhoid patients. Typically relapsing patients have an isolate with an antimicrobial susceptibility pattern identical to that during the first episode and can be managed with the same drug (82, 83). Reinfection has also been described and is distinguished by differences in the susceptibility pattern, Vi phage type, or molecular type of isolates (82–84).

**(iii) Fecal shedding and chronic carriage.** Most patients with acute enteric fever continue to excrete *Salmonella* serovar Typhi or Paratyphi A in their stool or urine for some days after starting antimicrobial treatment, and up to 10% may do so for up to 3 months. Approximately 1 to 4% of patients still excrete the organism at 3 months and are unlikely to cease shedding. Those excreting at 1 year meet the formal definition of “chronic carrier.” Among carriers detected by screening, one-quarter give no history of acute typhoid fever. Fecal carriage is more frequent among individuals with gallbladder disease and is most common among women over 40 years of age. In the Far East there is an association between fecal carriage and opisthorchiasis, and urinary carriage is associated with schistosomiasis and nephrolithiasis. Most chronic carriers have no symptoms, although acute typhoid fever has been reported among carriers on occasions. Chronic carriage can occur with both *Salmonella* serovar Typhi and Paratyphi A (85). Chronic *Salmonella* serovar Typhi carriers have an increased risk of carcinoma of the gallbladder (86, 87). In one of the few attempts to measure the prevalence of *Salmonella* serovar Typhi carriage in a population, in Santiago, Chile, in 1980, there were estimated to be 694 chronic carriers per 100,000 population (88).

The detection of chronic carriers depends on the labor-intensive isolation of the bacteria from stool or urine. Excretion can be

intermittent, and at least three negative stool cultures are required for patients to be considered free of infection (89). Identification of carriers of *Salmonella* serovar Typhi can be accomplished by serial stool culture. The detection of IgG to the Vi antigen has been proposed as a method to detect chronic carriers, and the test has proved valuable in the context of outbreak investigations (90–93). Its role in detecting carriers in the general population of areas of endemicity where background levels of IgG to Vi may be high, or where the Vi vaccine is widely used, is less clear (94). Nucleic acid amplification tests of gallbladder contents may be a diagnostic addition in the future (95).

**Prevention and control.** Enteric fever in Western Europe and North America declined in parallel with the introduction of treatment of municipal water, pasteurization of dairy products, and exclusion of human feces from food production (96). More recently declines have occurred in Latin America (4) and in some Asian countries (97) in parallel with economic transition and water and sanitation improvements. Strategies for enteric fever prevention include improving sanitation, ensuring the safety of food and water supplies, identification and treatment of chronic carriers of *Salmonella* serovar Typhi, and the use of typhoid vaccines to reduce the susceptibility of hosts to infection or disease. Reducing the proportion of people without access to safe drinking water is a component of Millennium Development Goal 7 (98).

Two typhoid vaccines are currently available in the United States. The Ty21a vaccine is a live, attenuated, oral vaccine containing the chemically attenuated *Salmonella* serovar Typhi strain Ty21a, and the parenteral Vi vaccine is based on the *Salmonella* serovar Typhi Vi capsular polysaccharide antigen. Ty21a is available as orally administered enteric capsules and is licensed in the United States for use in children  $\geq 6$  years of age and elsewhere for children as young as 2 years of age. The Vi-based vaccine is licensed in the United States for children aged  $\geq 2$  years. The cumulative protective efficacy over 3 years has been estimated to be 48% for Ty21a and 55% for Vi polysaccharide vaccine in a Cochrane systematic review (99). The effectiveness of the parenteral Vi vaccine has recently been confirmed in young children, and the protection of unvaccinated neighbors of Vi vaccinees has been demonstrated (100). The earliest Vi conjugate vaccine to reach clinical trials, Vi-rEPA, has been shown to be safe and immunogenic in Vietnamese children aged 2 to 5 years, providing protective efficacy of 91.5% (101) and an estimated 89% cumulative efficacy after 3.8 years (99). Phase 2 studies of other Vi conjugate vaccines have been completed (102). A number of Vi conjugate constructs are now in development. However, Vi-based monovalent vaccines do not offer protection against most paratyphoid fever, because only *Salmonella* serovars Typhi, Paratyphi C, and Dublin carry the Vi antigen. *Salmonella* serovar Typhi Ty21a does not express the Vi antigen, and clinical field trials suggest that while Ty21a may provide limited protection against *Salmonella* serovar Paratyphi B, it does not offer cross-protection against *Salmonella* serovar Paratyphi A (103, 104). The development of effective vaccines for paratyphoid fever is an important priority.

### Nontyphoidal *Salmonella*

**Burden of disease.** In industrialized countries, nontyphoidal *Salmonella* is transmitted predominantly by commercially produced food contaminated by animal feces, and it usually causes a self-limited enterocolitis with diarrhea in humans. Bloodstream infection occurs in approximately 6% of patients with diarrheal

enterocolitis; infants, young children, the elderly, and the immunocompromised are at particular risk for bacteremia (105–108). Nontyphoidal *Salmonella* serovars are diverse in their host range and epidemiology and vary in their propensity to cause bloodstream infection and severe human disease. *Salmonella* serovar Typhimurium is considered to be a typical host generalist with a broad host range and modest likelihood of causing invasive disease, while other nontyphoidal *Salmonella* serovars such as *Salmonella* serovars Heidelberg, Dublin, and Choleraesuis are markedly more likely than *Salmonella* serovar Typhimurium to cause hospitalization, invasive disease, or death. Some serovars, such as *Salmonella* serovar Newport, are associated with a lower case fatality ratio (0.3%) than *Salmonella* serovar Typhimurium (108, 109). The reasons for differences in host specificity among *Salmonella* serovars are complex and incompletely understood. Genome degradation appears to be associated with host specificity in *Salmonella* Typhi and *Salmonella* Paratyphi A, which have absent and deactivated genes compared with *Salmonella* Typhimurium. In addition, typhoidal *Salmonella* serovars elicit a dampened immune response compared with nontyphoidal *Salmonella* serovars associated with diarrhea and also produce a unique exotoxin, which may explain differences in the clinical phenotype (110, 111).

Modes of nontyphoidal *Salmonella* transmission in low- and middle-income countries are less well understood than in industrialized countries. Malaria and malnutrition predispose to invasive disease among children, and HIV does so among both children and young adults (3). Worldwide in 2006, enteric NTS was estimated to cause 93.8 million diarrheal illnesses and 155,000 deaths (112). In the Institute for Health Metrics and Evaluation Global Burden of Disease 2010 project, enteric nontyphoidal *Salmonella* was estimated to account for 4.8 million disability-adjusted life years (5) and 81,300 deaths (6). In 2010, nontyphoidal *Salmonella* was estimated to cause approximately 3.4 million invasive infections and 681,000 deaths; 57% of these illnesses and deaths occurred in Africa (113).

The most widely reported serovars associated with invasive disease across Africa are *Salmonella* serovar Typhimurium and *Salmonella* serovar Enteritidis (114–123). Some serovars are prominent in localized areas, such as *Salmonella* serovar Concord in Ethiopia (124), *Salmonella* serovar Bovismorbificans in Malawi (125), *Salmonella* serovar Stanleyville and *Salmonella* serovar Dublin in Mali (126), and *Salmonella* serovar Isangi in South Africa (127), the last being associated with a nosocomial outbreak.

A novel *Salmonella* serovar Typhimurium multilocus sequence type, ST313, has been described and currently accounts for much invasive disease in sub-Saharan Africa. This sequence type has a unique prophage repertoire and a degraded genome that shows some convergence with that of *Salmonella* serovar Typhi, raising the possibility of increased host specialization or invasiveness (128). One putative virulence gene, *ST313td*, has been described in *Salmonella* serovar Typhimurium ST313 and also found in other human invasive and enteric pathovars, notably *Salmonella* serovar Dublin (129). However, to date no other candidate virulence genes have been associated with invasive nontyphoidal *Salmonella* strains from HIV-infected patients (130). Ongoing genomic and phenotypic investigations of *Salmonella* serovar Typhimurium ST313 from Africa may be an area promising further new insights.

**Sources and modes of transmission.** While sources and modes

of transmission of enteric nontyphoidal *Salmonella* have been studied extensively in industrialized countries (131), epidemiologic studies of nontyphoidal *Salmonella* infections in areas of endemicity in sub-Saharan Africa are very limited (132). In industrialized countries, animal products and, increasingly, produce contaminated with animal feces are important sources of nontyphoidal *Salmonella* (131). Contact with animals, such as reptiles, and with animal environments are important sources of nontyphoidal *Salmonella* infection not associated with food (133). Although transmission by food contaminated with animal feces must be considered, greater roles than in industrialized countries for waterborne transmission, transmission directly from animals and their environments, and transmission between people, independent of a nonhuman animal reservoir, have been hypothesized. Partial genome molecular studies of nontyphoidal *Salmonella* strains from invasive human infections and those carried by animals among the households of children with invasive disease in Africa have so far failed to find similarities between strains, while family members of index cases have been found to have more closely related isolates (134, 135). Although it was hypothesized that the degraded genome of *Salmonella* serovar Typhimurium ST313 might reflect a reduced host range and human restriction of the sequence type, recent studies have indicated that ST313 also displays a severe invasive phenotype in chickens but reduced potential for cecal colonization (136). The emergence of two distinct clades of *Salmonella* serovar Typhimurium ST313 across Africa shows temporal relationships to acquired antimicrobial resistance determinants, particularly to the first-line antimicrobial chloramphenicol, and to the emergence of HIV on the continent (137). This suggests that transmission among humans may have exerted genomic selection pressure. Little is known about the epidemiology or phenotype of prevalent enteric nontyphoidal *Salmonella* strains in Africa. Nontyphoidal *Salmonella* was not a common cause of moderate to severe diarrheal disease in African sites participating in the Global Enterics Multicenter Study (138). However, asymptomatic carriage of nontyphoidal *Salmonella* appears to be relatively common (134, 138). The contribution to asymptomatic carriage or diarrheal disease in Africa of *Salmonella* serovar Typhimurium ST313 is still unclear, although the diversity of nontyphoidal *Salmonella* strains from enteric samples is likely to be wide (139).

**Host risk and protective factors.** Previous gastric surgery, pernicious anemia, and medications that reduce the acid barrier, such as antacids, H<sub>2</sub> antagonists, and proton pump inhibitors, increase susceptibility to nontyphoidal *Salmonella* enteric infection (140–144). Individuals at the extremes of age are at increased risk of invasive nontyphoidal *Salmonella*. In the case of older people, this may be because of multiple comorbidities, including diabetes, renal disease, or medications. The recent use of antimicrobials is associated with increased risk of multidrug-resistant *Salmonella* infection (145).

In Africa, there is a clear bimodal age distribution that contrasts with the continuous age distribution through childhood to adulthood of typhoid fever. Children aged from 6 to 18 months and adults aged 25 to 40 years, in whom HIV prevalence is also highest, show the highest incidences of invasive nontyphoidal *Salmonella* in Africa (146). Among children, there is a relatively low incidence of invasive nontyphoidal *Salmonella* below the age of 6 months. This may be attributable to protection afforded by breastfeeding, by lack of exposure to contaminated water or food during

exclusive breastfeeding, or by transplacental transfer of protective IgG (147). However, neonatal invasive nontyphoidal *Salmonella* does occur, particularly among children born outside a health care facility (148, 149).

Unlike enteric fever, for which there are no clear clinical associations with classic immunocompromising conditions, invasive nontyphoidal *Salmonella* is associated with many forms of immunocompromise (150). These include disorders of oxidative cellular killing, such as chronic granulomatous disease, in which nontyphoidal *Salmonella* is described as the most common cause of bloodstream infection and the third leading cause of all infections (151). Children who are homozygous for sickle cell disease are susceptible to invasive nontyphoidal *Salmonella* infections (152). In addition, inherited deficiencies of cytokines that are known to be critical for intracellular killing, particularly interleukin-12 (IL-12) and IL-23, are associated with invasive nontyphoidal *Salmonella* (153).

There is an overwhelming association of invasive nontyphoidal *Salmonella* with advanced HIV disease among African adults, with >95% of cases being HIV infected (1, 122, 150, 154–157). Among children, HIV is a risk factor (OR, 3.2) for infection with NTS (158). In cohorts of African children with invasive nontyphoidal *Salmonella*, around 20% are typically HIV infected (116). Several immune defects have been described that could contribute to the apparent exquisite susceptibility of adults with advanced HIV to recurrent invasive nontyphoidal *Salmonella*. These include the loss of IL-17-producing CD4 cells in the gut mucosa, permitting rapid invasion (159), and dysregulated excess production of anti-LPS IgG that inhibits serum killing of extracellular *Salmonella* in a concentration-dependent fashion (160, 161). Nontyphoidal *Salmonella* establishes an intracellular niche during invasive disease in HIV infection (162). It is likely that this is facilitated by the ability of the bacteria to be rapidly internalized before serum killing can occur (163). Once in the intracellular niche, reduction and dysregulation of proinflammatory cytokine responses in HIV-infected individuals, observed *in vivo* (162, 164) and *ex vivo* (165), allow intracellular survival and persistence, leading to frequent recrudescence and relapses of bacteremia with identical strains of nontyphoidal *Salmonella* (154, 166). In contrast with HIV-infected adults, a lack of protective antibody appears to be implicated in the susceptibility of African children <18 months of age to invasive nontyphoidal *Salmonella* disease, and antibody is likely to be important both for cellular and cell-free control of nontyphoidal *Salmonella* disease in children (147, 167, 168).

An association of invasive nontyphoidal *Salmonella* with malaria among African children was first noted in 1987 in West Africa (117). Since then, recent malaria (116), acute severe malaria (169), and severe malarial anemia, but not cerebral malaria (170), have all been specifically described as risk factors for invasive nontyphoidal *Salmonella*. The co-relationship of malaria with invasive nontyphoidal *Salmonella* among children has also been described both spatially, contrasting high- and low-incidence areas for malaria (171, 172), and temporally, with both rising (172) and falling (173, 174) background incidences of malaria being associated with corresponding changes in the incidence of invasive nontyphoidal *Salmonella*. However, this association is not necessarily specific for invasive nontyphoidal *Salmonella*, and a strong association of malaria with all bacteremias has been noted in Kenyan children, where the bacteremia incidence rate ratio associated with malaria parasitemia is 6.69 (175). A causal relationship with

malaria was inferred by a reduced odds ratio for sickle cell trait, which is protective against malaria, among children with bacteremia, particularly due to Gram-negative organisms (175).

Malnutrition is also associated with invasive nontyphoidal *Salmonella* in African children (116, 176). In rural Kenya, nontyphoidal *Salmonella* bacteremia was associated with child malnutrition, with an odds ratio (95% confidence interval) of 1.68 (1.15 to 2.44) (158). Invasive nontyphoidal *Salmonella* disease is strongly seasonal among both adults and children, coinciding with the rainy season (114). It is not clear whether this reflects waterborne transmission, seasonal malaria transmission during periods of increased rainfall, associated food scarcity and malnutrition, or a combination of these factors.

**Presenting symptoms and signs.** The clinical presentation of invasive nontyphoidal *Salmonella* infection is nonspecific among both children and adults. Therefore, recognition and management are challenging, particularly in settings without facilities for the laboratory diagnosis of bloodstream infection. Invasive nontyphoidal *Salmonella* presents as a febrile illness. Respiratory symptoms are frequently present, and diarrhea is often not a prominent feature. However, often the clinician is faced with a febrile patient without an obvious clinical focus of infection. Features on physical examination include abnormal respiratory findings, such as rapid respiratory rate or chest crepitations suggestive of pneumonia, and hepatosplenomegaly in 30 to 45% of cases (116, 154, 177, 178). Splenomegaly has been shown to be a useful clinical feature to predict nontyphoidal *Salmonella* bacteremia among adults in areas where HIV seroprevalence is high (179). The lack of current or recent diarrhea in invasive nontyphoidal *Salmonella* infection among immunosuppressed patients has been well described in many settings (180, 181). Patients with invasive nontyphoidal *Salmonella* also often display the features of underlying conditions such as anemia, malnutrition, and advanced HIV disease. It has been widely recognized that the nonspecific presentation among children often fulfills empirical algorithms for lower respiratory tract infection. In such circumstances, health care workers may commence antimicrobial treatment that is inappropriate for invasive nontyphoidal *Salmonella*, especially when antimicrobial resistance among *Salmonella enterica* is common (182, 183). In addition, febrile presentations are often not identified as bloodstream infection by pediatric guidelines (184, 185), resulting in delayed or missed antimicrobial treatment.

**Patient outcomes.** Nontyphoidal *Salmonella* meningitis may occur among children. It has poor outcomes and a high case fatality ratio (186). Although lower respiratory tract infection-related symptoms and signs are common in invasive nontyphoidal *Salmonella* infection, these are frequently caused by other pathogens (154). Lobar pneumonia caused by nontyphoidal *Salmonella* has been described in a child (187).

Recurrent invasive nontyphoidal *Salmonella* infection was quickly recognized as a defining feature of AIDS in the 1980s. Recurrence typically occurs in 20 to 30% of treated adults with HIV, usually within 4 to 6 months (154, 162). Partial- and whole-genome sequencing has been used to establish that 80% of cases of recurrence are due to recrudescence with an identical strain, likely arising from intracellular persistence and latency. Only 20% of recurrences represent reinfection with a new strain (154, 166). Patients with HIV infection, once established on effective antiretroviral treatment after an episode of invasive nontyphoidal *Salmonella*, appear to be less likely to experience recurrence (188). In

areas where HIV seroprevalence is not high, persistent nontyphoidal *Salmonella* bacteremia may suggest mycotic aneurysm. Nontyphoidal *Salmonella* intravascular, bone, and joint infections are frequently reported in industrialized countries (189).

Mortality from invasive nontyphoidal *Salmonella* infection is high in all subgroups, even if appropriate antimicrobial therapy is given. Case fatality ratios among HIV-infected adults from African case series were  $\geq 50\%$  early in the HIV epidemic (122, 154). A study from Thailand reported a case fatality ratio of 36% among all cases of invasive nontyphoidal *Salmonella* but 59% among cases who were HIV infected (190). The reported case fatality ratio among adults appears to have fallen gradually in Africa, after initial reports in the 1980s and 1990s, to around 20 to 25% more recently. This has been attributed largely to improved recognition and more prompt and effective management (191). It is possible but not certain that more-effective antimicrobials, such as fluoroquinolones replacing chloramphenicol, may also have contributed to these improving outcomes (114). More recently, with the wide availability of HIV care and treatment services, including antiretroviral therapy, across Africa, there are reports of a reduced incidence of and mortality from invasive nontyphoidal *Salmonella* and other bloodstream infections among adults (192). The case fatality ratio among cohorts of children with invasive nontyphoidal *Salmonella* disease across Africa has been reported to be 20 to 28% and highest among children  $< 2$  years of age. This is comparable to the case fatality ratio associated with other bloodstream infections (116, 158, 177).

**Prevention and control.** Food safety from farm to fork is fundamental to the control of nontyphoidal *Salmonella* in industrialized countries. The very limited evidence base on sources and modes of transmission of nontyphoidal *Salmonella* in low- and middle-income countries hampers the development of evidence-based prevention advice. However, some host risk factors for invasive nontyphoidal *Salmonella* disease are modifiable, and interventions to prevent these mitigate disease risk. Efforts to prevent and effectively manage malaria are likely to be important in this regard. Indeed, the prevalence of invasive nontyphoidal *Salmonella* has declined in parallel with that of malaria in a number of areas (173–175). HIV care and treatment services, including the use of trimethoprim-sulfamethoxazole prophylaxis to prevent opportunistic infections (193, 194) and antiretroviral therapy to reverse immunosuppression, are likely to reduce the risk for invasion by nontyphoidal *Salmonella* and in turn disease incidence (188, 195).

Despite invasive nontyphoidal *Salmonella* being overlooked in evaluations of disease burden to date (5, 6, 196), some vaccine development efforts are under way (197). However, despite their availability for livestock and poultry, there are currently no nontyphoidal *Salmonella* vaccines available for humans. The occurrence of invasive nontyphoidal *Salmonella* disease predominantly among immunocompromised persons challenges vaccine development (160, 198).

### Challenge of Distinguishing Invasive *Salmonella* Infections from Other Febrile Conditions in Areas of Endemicity

In settings where enteric fever and invasive salmonellosis are endemic, most patients with fever self-treat by visiting a local pharmacy or shop selling antimicrobials. Those who do not respond to self-treatment may then present to a health center, outpatient clinic, or hospital. Many other viral, bacterial, and protozoal in-



TABLE 2 Modifications of blood culture methods to improve detection of *Salmonella* Typhi and *Salmonella* Paratyphi A

Methodological issue	Method <sup>a</sup>	Advantages	References
Formulation of broth blood culture medium	Bile salt broth/Oxgall	Bile salts and Oxgall inhibit bactericidal activity of blood, improve detection of <i>Salmonella</i> Typhi and <i>Salmonella</i> Paratyphi A, unsuitable for isolation of non-enteric fever pathogens	212–215, 219
	Supplementation of BHI broth or TSB with 0.05% SPS	SPS inhibits bactericidal activity of blood	213, 214, 220
	Soybean casein digest broth (Bactec system)	Automated detection, quality-assured medium, expense, complete system includes automated culture instrument	216–218
	Peptone-enriched TSB supplemented with BHI solids (BactAlert)	Charcoal or resins in the medium should adsorb antimicrobials	216, 218
	Inclusion of charcoal or resins in the medium to adsorb antimicrobials	Reduce bactericidal activity of blood and dilute antimicrobials present	221
Sample used	Blood-to-broth dilution ratio: at least 1:10 is important, although higher dilutions may be beneficial		
	Clot culture: blood clot, after separation from serum, added to preprepared streptokinase broth	Removal of serum thought to reduce bactericidal activity of blood, improved yield even when on chloramphenicol treatment	213, 221–225
	Lysis of cells in blood before start of culture	May release intracellular bacteria	226, 227
Duration of incubation	Centrifugation of blood followed by direct culture on solid medium	May concentrate low numbers of bacteria and produce the bacteria growing on the plate more quickly	226, 227
	Prolonging duration of blood culture incubation	Incubation duration of longer than 7 days increased yield in older blood cultures systems; modern continuously monitored automated systems usually positive within 48 h	204, 220

<sup>a</sup> BHI, brain heart infusion; TSB, tryptic soy broth; SPS, sodium polyethanol sulfonate.

fections resemble enteric fever and invasive salmonellosis (9). Enteric fever and invasive nontyphoidal salmonellosis should always be considered when suspected malaria has not been confirmed or the illness has not responded to antimalarial therapy. In areas of endemicity, rickettsial infections, leptospirosis, brucellosis, and dengue should be considered in the differential diagnosis. Noninfectious conditions characterized by fever, including lymphoproliferative disorders and vasculitides, should not be overlooked. Clinical judgment can be unreliable, and broad-spectrum antimicrobials may be needed in the initial management of severely ill febrile patients. A few clinical algorithms have been developed for febrile disease diagnosis (199–202), but these are limited by a lack of accuracy.

### LABORATORY DIAGNOSIS

Diagnostic tests are needed for the diagnosis of invasive *Salmonella* infections, for the detection of convalescent and chronic fecal carriage of typhoidal *Salmonella*, and to estimate the burden of disease for public health assessment. Different tests and biological samples may be required for each situation (203). It may be important to be able to detect both *Salmonella* serovar Typhi and *Salmonella* serovar Paratyphi A infections, as they cannot be distinguished from each other clinically. Microbial culture is the mainstay of diagnosis. Antibody and antigen detection and nucleic acid amplification tests have limitations, as described below.

### Bacterial Culture

The definitive diagnosis of enteric fever relies on the isolation of *Salmonella enterica* from normally sterile clinical samples, usually blood and bone marrow. Culture confirms the diagnosis and provides an isolate for antimicrobial susceptibility testing, epidemiologic typing, and molecular characterization. In untreated pa-

tients with enteric fever, the blood culture is positive in 80% of patients or more (41, 204, 205). In areas of endemicity where antimicrobials are frequently taken before evaluation, the yield from blood culture can be as low as 40%, and in this setting, bone marrow aspirate culture is usually considered the reference standard method, with a sensitivity of >80%. The importance of the volume of blood taken for blood culture relates to the number of bacteria in the blood (211). Invariably, the number of viable bacteria in each milliliter of blood is less than 10, and frequently it is only one or less (162, 206–210). The optimum period for detecting organisms circulating in the bloodstream is considered to be in the first or second week of the illness, although cultures can still remain positive in the third week in the absence of antimicrobial exposure (41, 204, 207). Quantitative bacteriology studies have shown declining counts with an increasing duration of disease (210). Various methods are used to improve the yield of blood culture (summarized in Table 2), but all remain limited by the low numbers of viable bacteria in blood.

A number of studies have demonstrated a higher sensitivity from bone marrow culture aspirate than from blood culture, even after antimicrobials have been taken for several days and regardless of the duration of disease prior to sampling (162, 215, 228–233) (Table 3). The increased sensitivity of bone marrow culture compared with blood culture relates to the higher bacterial concentration in bone marrow (234). Bone marrow culture is more frequently positive in patients with severe and complicated disease (226). A bone marrow aspiration is an uncomfortable and specialized procedure, uncommonly performed outside research studies, although some authors have suggested that a fine-needle technique can be well tolerated (235). It is notable that most studies demonstrating a higher yield from bone marrow were performed

TABLE 3 Sensitivity of blood culture versus bone marrow culture for the diagnosis of enteric fever

Author(s) (reference)	Yr published	No. of samples tested (blood and bone marrow culture)	Blood culture			Bone marrow culture			Culture system	No. (%) positive
			Vol (ml)	Culture medium	Culture system	Vol (ml)	Culture medium	No. (%) positive		
Hirowitz and Cassel (599)	1951	28	NA <sup>a</sup>	Ox bile broth	Manual	13 (46.4)	NA	Ox bile broth	Manual	18 (64.3)
Gilman et al. (228)	1975	62	2	Supplemented peptone broth	Manual	25 (40.3)	NA	Supplemented peptone broth, Ruiz-Castaneda	Manual	56 (90.3)
Guerra-Caceres et al. (229)	1979	60	15	Trypticase soy broth, Ruiz-Castaneda	Manual	26 (43.3)	0.5–1.0	Trypticase soy broth, Ruiz-Castaneda	Manual	57 (95.0)
Benavente et al. (236)	1984	36	3	Ox bile broth	Manual	15 (41.7)	0.5–1.0	Ox bile broth	Manual	27 (75.0)
Hoffman et al. (215)	1984	118	3	Ox bile broth	Manual	64 (54.2)	0.5–0.8	Ox bile broth	Manual	101 (85.6)
Vallenas et al. (230)	1985	43	3	Ox bile broth	Manual	19 (44.2)	0.5	Ox bile broth	Manual	36 (83.7)
Hoffman et al. (231)	1986	61	3	Ox bile broth	Manual	27/56 (48.2)	NA	Ox bile broth	Manual	56/61 (91.8)
Hoffman et al. (231)	1986	61	8	Ox bile broth	Manual	38/56 (67.9)	NA	Ox bile broth	Manual	56/61 (91.8)
Rubin et al. (209)	1990	29	8	Ox bile broth	Manual	14 (48.3)	0.5–0.8	Ox bile broth	Manual	25 (86.2)
Akoh (233)	1991	31	2	Thioglycolate broth	Manual	11 (35.4)	1.0–2.0	Thioglycolate broth	Manual	19 (61.3)
Dance et al. (600)	1991	17	15	Brain heart infusion broth with sodium polyanethol sulfonate	Manual	14 (82.4)	0.5–1.0	Brain heart infusion broth with sodium polyanethol sulfonate	Manual	15 (88.2)
Farooqui et al. (232)	1991	88	5	Brain heart infusion broth, thioglycolate broth	Manual	58 (65.9)	0.5–1.0	Brain heart infusion broth, thioglycolate broth	Manual	88 (100)
Chaicumpa et al. (292)	1992	52	3	Ox bile broth	Manual	22 (42.3)	0.5–0.8	Ox bile broth	Manual	32 (61.5)
Gasem et al. (601)	1995	86	3	Ox bile broth	Manual	57 (66.3)	1.0	Ox bile broth	Manual	70 (81.4)
Gasem et al. (601)	1995	86	10	Ox bile broth	Manual	58 (67.4)	1.0	Ox bile broth	Manual	70 (81.4)
Gasem et al. (602)	2002	53	8–10	Becton Dickinson Bactec/F medium	Continuously monitored	43 (81.1)	1.0–2.0	Becton Dickinson Bactec/F medium	Continuously monitored	53 (86.9)
Wain et al. (214)	2008	73	5	Brain heart infusion broth, brain heart infusion broth with sodium polyanethol sulfonate, ox bile broth	Manual	57 (78.1)	1.0	NA	Manual	69 (94.5)
Wain et al. (214)	2008	68	15	Brain heart infusion, brain heart infusion with sodium polyanethol sulfonate, ox bile broth	Manual	59 (86.7)	1.0	NA	Manual	61 (89.7)

<sup>a</sup> NA, not available.

before modern blood culture media and continuously monitored blood culture instruments were available and generally used low volumes of blood for culture (232, 233). It is possible that if a sufficiently large volume of blood is taken for culture using modern media and systems (211), blood culture may be as sensitive as bone marrow culture. Rose spot culture has been reported to be positive in 70% of patients, although in practice rose spots are rarely present (228). Cerebrospinal fluid culture is usually positive only in very young children (62).

*Salmonella enterica* may be isolated from feces in up to 30% of patients with typhoid fever and in <1% of urine samples, with the number of organisms recoverable from feces increasing throughout an untreated illness (41). The sensitivity of fecal culture increases from about 10% in a single sample to about 30% by testing multiple samples. Sensitivity is also improved by using whole feces rather than rectal swabs and by using a Selenite F enrichment step and selective media. Culture of bile obtained from an overnight duodenal string capsule provides a sensitivity similar to that for blood culture and offers an additional means to isolate typhoidal *Salmonella* from patients or carriers. Young children and those with severe disease may be unable to tolerate the procedure (215, 230, 236). A positive culture from feces, duodenal contents, or urine requires cautious interpretation. Although it may indicate acute enteric fever infection, it could also represent chronic carriage, with the acute infection syndrome caused by a different organism.

Isolates of *Salmonella* serovar Typhi and *Salmonella* serovar Paratyphi A should be handled with care in the laboratory, as they have been a common cause of laboratory-acquired infection. Many jurisdictions recommend handling these pathogens under biosafety level 3 conditions. Adequate disposal of specimens and cultures by autoclaving is essential.

### Serologic Assays

**Antibody detection.** The Widal test measures agglutinating antibodies against LPS (O) and flagellar (H) antigens of *Salmonella* serovar Typhi in the sera of individuals with suspected enteric fever (237). Although usually discouraged due to inaccuracy, it is simple and inexpensive to perform and is still widely used in some countries (238). The performance of the method has been hampered by a lack of standardization of reagents and inappropriate result interpretation (239, 240). The Widal test ideally requires both acute- and convalescent-phase serum samples taken approximately 10 days apart; a positive result is determined by a 4-fold increase in antibody titer. However, antibody titers in infected patients often rise before the clinical onset, making it difficult to demonstrate the required 4-fold rise between initial and subsequent samples (237, 241). In practice, the result from a single, acute-phase serum sample is often used, but false-negative and false-positive results are common. Knowledge of the background levels of antibodies in the local population may aid interpretation of the Widal test, and performance is best among patients with a high prior probability of enteric fever (242, 243). For example, in a study from Vietnam using Widal test data from patients with typhoid fever and both febrile and healthy control participants, it was found that a cutoff titer of  $\geq 200$  for O agglutination or  $\geq 100$  for H agglutination would correctly diagnose 74% of blood culture-positive patients. However, 14% of positive results were classified as false positive and 10% of negative results as false negative (243).

Enzyme-linked immunosorbent assays (ELISAs) have been used to study the normal antibody response during enteric fever to LPS, flagella, Vi capsular polysaccharide, or outer membrane protein antigens (244–251). Although ELISAs measuring anti-LPS antibodies and anti-flagellum antigens are more sensitive than the Widal “O” and “H” antigen-based test, the results are still limited by lack of specificity. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting has also been used to detect serum antibodies against LPS and flagellar antigens of *Salmonella* serovar Typhi and *Salmonella* serovars Paratyphi A, Paratyphi B, and Paratyphi C (252).

**Rapid serologic tests.** There are a number of commercially available point-of-care rapid serologic tests for enteric fever. Their characteristics are summarized in Table 4 and in a recent review (253). The tests currently available have different methods and formats. Most have been developed for use with blood, including venous whole-blood, serum, or capillary samples, and detect antibody directed against *Salmonella* antigens. The antibody class detected is usually IgM, which is suggestive of a current or recent infection. Some rapid tests detect IgG, which may indicate a current infection or previous exposure.

Typhidot (Malaysian Biodiagnostic Research Sdn Bhd, Kuala Lumpur, Malaysia) detects specific IgM and IgG antibodies against a 50-kDa *Salmonella* serovar Typhi outer membrane protein (OMP) in an immunodot test format. Typhidot-M is a modified version of Typhidot but detects IgM to the same OMP and as a more specific marker of current acute infection (254–260). Reported sensitivities vary between 67 and 98% for Typhidot and between 47 and 98% for Typhidot-M, with specificities of 73 to 100% for Typhidot and 65 to 93% for Typhidot-M. The Typhi-Rapid IgM and TyphiRapid IgG IgM (Combo) are similar versions of the test but in an ICT cassette format (261, 262). Tubex TF (IDL Biotech, Sollentuna, Sweden) detects antibody against *Salmonella* serovar Typhi LPS with an inhibition assay format and visual result readout (249, 256–260, 263). Reported sensitivities for Tubex TF vary between 56 to 100%, with specificities of 58 to 100%. A modification for paratyphoid diagnosis has recently been developed (264). The Royal Tropical Institute (KIT), Netherlands, has developed a test detecting IgM against LPS using a dipstick, latex agglutination, and, most recently, a lateral-flow format (Life-Assay, Cape Town, South Africa) (249, 265, 266). Studies using the lateral-flow test report sensitivities of 60% and specificities of 98%. Other rapid test kits available include the following: an ELISA and dipstick (Multi-Test Dip-S-Ticks) from PanBio (PanBio Indx, Inc., Baltimore, MD) detecting anti-LPS IgG and IgM; Mega-Salmonella (Mega Diagnostics, Los Angeles, CA), which is an ELISA detecting IgG and IgM antibodies against an undefined *Salmonella* serovar Typhi antigen; the SD Bioline Typhoid rapid test (Standard Diagnostics, Kyonggi-do, South Korea), which uses an immunochromatographic method to detect IgG and IgM antibodies against another undefined *Salmonella* serovar Typhi antigen; and a dipstick test named Enterocheck-WB (Zephyr Biomedicals, Goa, India) that detects anti-LPS IgM antibodies (257, 259, 267, 268). A number of other tests are commercially available but have not been evaluated in published studies.

Although rapid serologic tests may represent some improvement over the Widal test, currently available results suggest that they still lack sensitivity and also specificity because of the background antibody levels in the general population (269) and the cross-reactive nature of the selected antigens. Accurate evaluation

**TABLE 4** Characteristics of selected serologic tests used for the diagnosis of infection with *Salmonella* Typhi and *Salmonella* Paratyphi A

Test	Test methodology	Reported characteristics <sup>b</sup>	Reference(s)
Enterocheck-WB	Dipstick detecting anti-LPS IgM antibodies	Sensitivity, 89%; specificity, 97%	268
LifeAssay Test-it	Detects IgM antibodies against <i>Salmonella</i> Typhi LPS in an ICT LFA cassette format	Sensitivity, 59%; specificity, 98%	265, 266
Mega <i>Salmonella</i>	ELISA detecting IgG and IgM antibodies against an undefined <i>Salmonella</i> Typhi antigen	Sensitivity, 91%; specificity, 49%	257
Multi-Test-Dip-S-Ticks	Dipstick detecting anti-LPS IgG and IgM	Sensitivity, 89%; specificity, 53%	259
PanBio	ELISA detecting anti-LPS IgG and IgM	Sensitivity, 78%; specificity, 80%	267
SD Bioline	ICT LFA cassette detecting IgG and IgM antibodies against an undefined <i>Salmonella</i> Typhi antigen	Sensitivity, 69%; specificity, 79%	257
Tubex TF	Detects antibody against <i>Salmonella</i> Typhi LPS with an inhibition assay format and a visual result readout	Sensitivity, 56–100%; specificity, 58–100%	249, 255–260, 263, 270
Typhidot	Measures IgM and IgG antibodies against a 50-kDa outer membrane protein of <i>Salmonella</i> Typhi in an immunodot test format	Sensitivity, 67–98%; specificity, 58–100%	254, 255, 257, 259, 260, 269
Typhidot M	Measures IgM antibodies, after removal of IgG antibodies, against a 50-kDa outer membrane protein of <i>Salmonella</i> Typhi in a dot blot format	Sensitivity, 47–98%; specificity, 65–93%	254, 255, 258
TyphiRapid IgM and IgG IgM (Combo)	Measures IgM antibodies, after removal of IgG antibodies, against a 50-kDa outer membrane protein of <i>Salmonella</i> Typhi in an ICT LFA <sup>a</sup> cassette format	Sensitivity, 89–100%; specificity, 85–89%	261, 262
Widal test	Measures agglutinating antibodies against O and H antigens of <i>Salmonella</i> Typhi and <i>Salmonella</i> Paratyphi A; uses a tube or slide format	Very variable sensitivity and specificity; lack of standardized reagents	237–240, 242, 243

<sup>a</sup> ICT, immunochromatographic test; LFA, lateral-flow assay.

<sup>b</sup> This column shows the range of sensitivity and specificity values from different studies with a range of sample sizes and methodologies. Where there is only one study, that value is given. For a systematic review of the studies examining Tubex TF and Typhidot, see reference 270.

of the tests is also hampered by the absence of a satisfactory reference standard. A recent systematic review of studies of two widely used tests, Tubex TF and Typhidot, concluded that the performance characteristics did not justify their use (270).

### Molecular Assays

Nucleic acid amplification tests, including conventional PCR and real-time PCR, have been developed for the detection of both *Salmonella* serovars Typhi and Paratyphi A, mainly in blood (271–288). Nucleic acid amplification methods have the potential to amplify small numbers of organisms and nonculturable bacteria, as well as dead organisms. Targets for *Salmonella* serovar Typhi PCR-based assays have included the Hd flagellin gene *fliC-d* (271), the Vi capsular gene *viaB* (272), the tyvelose epimerase gene (*tyv*) (previously *rfbE*), the paratose synthase gene (*prt*) (previously *rfbS*), *groEL* (273), the 16sRNA gene (*hilA*) (a regulatory gene in *Salmonella* pathogenicity island 1 [SPI-1]) (275), the gene encoding the 50-kDa outer membrane protein ST50 (276), and the hypothetical protein gene *ratA* (277). Nested primers have been used in some studies to improve sensitivity, although this may lead to unspecific amplification and contamination.

The sensitivity of PCR without enrichment in blood-culture positive cases has exceeded 90% in some studies (271, 273, 278–286), although other studies have reported much lower sensitivities more consistent with the number of bacteria in the blood (266, 272, 287). Bone marrow aspirates were examined in one study, with 100% sensitivity (287), and positive results have also been found in urine samples (288). The specificity among patients with other conditions has usually been 100%. Several studies have reported patients with clinically suspected typhoid who are PCR positive and blood culture negative (266, 272). The absence of a perfect reference standard makes interpretation of these results challenging.

### Other Diagnostic Tests

Assays to detect bacterial antigens such as Vi, O9, and Hd in urine have been used as diagnostic methods for enteric fever but with variable results (235, 289–293). The greatest level of sensitivity was found with the Vi antigen, whereas the O9 and Hd antigens were less sensitive. The sensitivity for Vi increased when multiple samples were examined, but the specificity was less satisfactory, particularly in patients with brucellosis. In studies of patients from Indonesia on detection of O9 antigen in urine using an ELISA and dot blot format, the sensitivity increased from 65% to 95% when between one and three urine samples were examined (292). In a further study in Vietnam, the sensitivity was 92% and specificity 72% when three serial urine samples were compared with blood culture (293). These data indicate the intermittent nature of antigen excretion in the urine during an infection. Studies detecting Vi and other antigens in serum have also been performed, with variable results (294–299).

### New Diagnostic Approaches

There is a considerable research effort aimed at developing new diagnostics for enteric fever (203). Increasing knowledge of the *Salmonella* serovar Typhi and *Salmonella* serovar Paratyphi A genomes should lead to better targets for nucleic acid amplification tests (300–303). Methods to remove potential inhibitory human DNA from the sample may improve sensitivity (304), as may combining short periods of blood culture broth incubation with PCR amplification (305). Proteomic and immunoscreening approaches are being used to seek antibodies and antigens that have a higher level of specificity than those used currently used (306–311). Analysis of bacterial gene expression in typhoid and paratyphoid may also lead to new diagnostic tests (312–314).

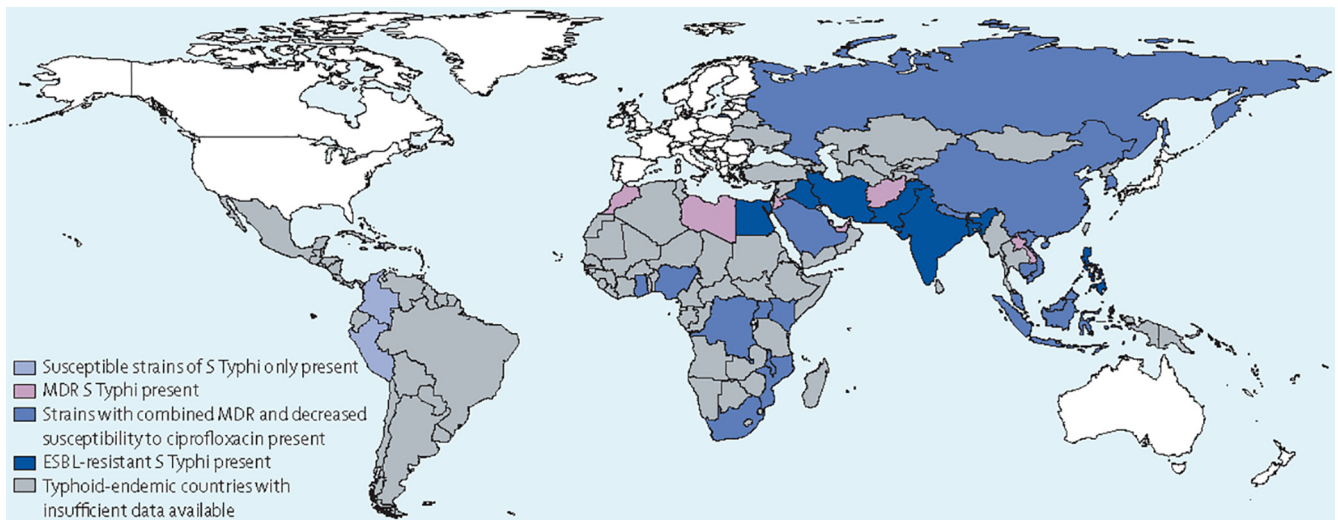


FIG 3 Worldwide distribution of antimicrobial drug resistance in *Salmonella enterica* serovar Typhi. (Reprinted from reference 604 with permission from Elsevier.)

### Other Laboratory Findings In Enteric Fever

Most patients with enteric fever have a total white cell count within the normal range. Leukocytosis may suggest an intestinal perforation or another diagnosis. Eosinopenia is a common although nonspecific finding (51). A normochromic anemia, mild thrombocytopenia, and an increased erythrocyte sedimentation rate are common. There may be laboratory markers of a mild disseminated intravascular coagulation, although this rarely appears to be of clinical relevance (208). Elevation of alanine transaminases and aspartate transaminase to two to three times the normal level is a frequent accompaniment (52).

### ANTIMICROBIAL RESISTANCE

#### Development of Antimicrobial Resistance among Typhoidal *Salmonella* Strains

Figure 3 summarizes the current global distribution of antimicrobial drug resistance in *Salmonella* Typhi. Prior to the mid-1970s, chloramphenicol was the mainstay of treatment of enteric fever (315–317). However, reports on chloramphenicol-resistant isolates began to appear before 1970 (318, 319). In 1972, the first epidemic caused by a chloramphenicol-resistant strain was reported from Mexico (320). Soon thereafter, outbreaks involving chloramphenicol-resistant *Salmonella* serovar Typhi were reported from several different areas, including India (321), Vietnam (322, 323), South Korea (324), and Bangladesh (325). A common feature of the outbreak strains was that the chloramphenicol resistance determinant was located on a self-transmissible plasmid of the HII incompatibility type (IncHI) (325, 326). In addition to chloramphenicol resistance, these plasmids often carried genes conferring resistance to other drugs, such as streptomycin, sulfonamides, and tetracyclines (325, 326).

The development of chloramphenicol resistance led to increased use of two other first-line drugs, ampicillin and trimethoprim-sulfamethoxazole. Trimethoprim-sulfamethoxazole remained an effective drug until 1975, when resistance was reported from France (327). By the late 1980s, multiple-drug resistance (MDR), defined as resistance to ampicillin, chloramphenicol, and trimethoprim-

sulfamethoxazole, was reported from multiple countries (328–330). Cases of enteric fever caused by MDR *Salmonella* serovars Typhi and Paratyphi A continued to emerge in the 1990s and early 2000s (331–336). Among *Salmonella* Typhi isolates collected in Vietnam in 1993 to 1996, 80% were reported to be MDR (82). A similar prevalence was reported from Africa among isolates collected in Kenya and Nigeria in 2004 to 2006 (70 and 61% MDR, respectively) (338, 339). In Europe, a large retrospective study looking at 692 *Salmonella* serovar Typhi isolates collected in 2002 to 2003 documented a 22% prevalence of the MDR phenotype (337). A study in Delhi, India, found that MDR *Salmonella* serovar Typhi increased from 34% in 1999 to 66% in 2005 (340). Today, MDR *Salmonella* Typhi is considered endemic in many developing countries, especially in areas of South and Southeast Asia.

In response to the development and spread of MDR *Salmonella* serovar Typhi, the use of fluoroquinolone antimicrobials such as ciprofloxacin was recommended as an alternative for the treatment of typhoid fever (325, 342). However, resistance among *Salmonella* serovar Typhi isolates developed within a short period, with the first case being reported in 1992 from the United Kingdom (343). This was soon followed by similar reports from other countries, such as South Korea, India, and Vietnam (344, 345). The first epidemic involving a fluoroquinolone-resistant *Salmonella* serovar Typhi isolate occurred in Tajikistan in 1997 (346). The same year, 60% of *Salmonella* serovar Typhi isolates in India displayed a MIC of  $\geq 2$   $\mu\text{g/ml}$  to ciprofloxacin (345). Similarly, an increase in *Salmonella* serovar Paratyphi A isolates with ciprofloxacin MICs of  $\geq 2$   $\mu\text{g/ml}$  was reported from New Delhi in 2000 (347), and a ciprofloxacin-resistant isolate with a MIC of 128  $\mu\text{g/ml}$  was isolated in Japan in 2002 (348). By 2008, there were reports of ciprofloxacin-resistant *Salmonella* serovar Typhi from multiple centers in India (349–352). In 2010, a tertiary hospital in Chandigarh, India, reported that 13.6% of isolates were ciprofloxacin resistant (353). In 2013, a tertiary care center in New Delhi reported that 37.9% of 344 typhoidal *Salmonella* isolates were ciprofloxacin resistant (354). In association with increased use of ciprofloxacin, several areas have observed a decline in chlor-

amphenicol resistance and MDR prevalence among both *Salmonella* serovar Typhi and Paratyphi A isolates (355). Although this is an encouraging trend, the reintroduction of chloramphenicol as first-line treatment would likely result in reemergence of MDR isolates.

Decreased susceptibility to fluoroquinolones, often associated with nalidixic acid resistance, has also been observed in countries where these infections are not endemic, where the majority of cases are associated with international travel. In 1999, decreased susceptibility to fluoroquinolones was detected in 23% of all *Salmonella* serovar Typhi isolates in the United Kingdom (356). In the United States, the proportion of nalidixic acid-resistant isolates increased from 19% in 1999 to 42% in 2004 and in Canada, nalidixic acid resistant isolates rose from 40% to 80% between 2000 and 2006 (357, 358). A similar trend was observed in the United Kingdom, where the proportion of *Salmonella* serovar Typhi isolates with decreased susceptibility to ciprofloxacin increased from 35% in 2001 to 70% in 2006 (359).

In areas with a high prevalence of both MDR and fluoroquinolone resistance, azithromycin, an azalide antimicrobial that has demonstrated good efficacy against uncomplicated enteric fever in multiple clinical trials (360), and extended-spectrum cephalosporins (e.g., ceftriaxone) tend to be used for the treatment of enteric fever. However, *Salmonella* serovar Typhi isolates displaying resistance to extended-spectrum cephalosporins have been described. For example, extended-spectrum  $\beta$ -lactamase (ESBL) enzymes of the SHV-12 and CTX-M types and an AmpC  $\beta$ -lactamase of the ACC-1 type have been reported among *Salmonella* serovar Typhi isolates from Germany, the Philippines, Bangladesh, and India (361–364). In 2013, an MDR isolate of *Salmonella* serovar Paratyphi A harboring a CTX-M-15  $\beta$ -lactamase was detected in a Japanese traveler returning from India (605). Similarly, there have been sporadic reports of azithromycin resistance. A recent study from India reported increasing prevalence of azithromycin resistance among typhoidal *Salmonella* isolates; among 344 isolates collected in 2010 to 2012, 7.3% were resistant to azithromycin using disk diffusion interpretive criteria suggested by the British Society for Antimicrobial Chemotherapy (BSAC) (354). Importantly, an increasing prevalence of azithromycin resistance was observed for both *Salmonella* serovars Typhi and Paratyphi A over the 2-year study period (354).

### Development of Antimicrobial Resistance among Nontyphoidal *Salmonella* Strains

As for typhoidal *Salmonella*, an increasing prevalence of antimicrobial resistance has been observed in nontyphoidal *Salmonella* over recent decades. An important trend has been the development of MDR among isolates of *Salmonella* serovar Typhimurium but also other serovars. The MDR phenotype in *Salmonella* serovar Typhimurium began to appear in the early 1980s in the United Kingdom, where it was closely associated with a specific phage type called definitive type 104 (DT104) (365). These isolates displayed resistance to five antimicrobial agents—ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline—a resistance phenotype commonly referred to as R-type ACSSuT. By the 1990s, this phenotype had been reported from several other countries in Europe as well as the United States, Canada, Israel, Turkey, and Japan (366, 367). However, *Salmonella* serovar Typhimurium with R-type ACSSuT has been declining in many countries since that time. In the United States, this phenotype

accounted for 35% of all *Salmonella* serovar Typhimurium isolates submitted to the U.S. National Antimicrobial Monitoring System (NARMS) in 1997. However, between 1998 and 2005 there was a steady decline from 32% to 22%, and in 2011 20% of all *Salmonella* serovar Typhimurium isolates collected from humans displayed this phenotype (368, 369).

Another important resistance trend among nontyphoidal *Salmonella* isolates has been the development of resistance to quinolones (i.e., nalidixic acid) and fluoroquinolones such as ciprofloxacin. Although nalidixic acid is not used for treatment, development of resistance to this drug is of clinical importance since it may be associated with reduced clinical effectiveness of fluoroquinolone treatments (370, 371). Reports of quinolone resistance among nontyphoidal *Salmonella* strains followed soon after the introduction of fluoroquinolones. In Denmark, quinolone resistance in *Salmonella* serovar Enteritidis increased from 0.8% in 1995 to 8.5% in 2000. In the early 2000s, a large European surveillance study including 27,000 isolates reported low-level fluoroquinolone resistance in 13% of *Salmonella* serovar Typhimurium, 8% of *Salmonella* serovar Enteritidis, 53% of *Salmonella* serovar Virchow, and 57% of *Salmonella* serovar Hadar (372) isolates. In Southeast Asia, several studies have documented the emergence of quinolone- and fluoroquinolone-resistant *Salmonella* strains. In 2009, a high prevalence of reduced susceptibility to ciprofloxacin was reported among *Salmonella* strains from the Philippines (15%), Singapore (25%), and Thailand (46.2%) (373). In 2011, 31% of isolates were fully resistant to ciprofloxacin in a study from Thailand (374). The prevalence of fluoroquinolone-resistant isolates in high-income countries has been found to be lower (107). Among 2,344 nontyphoidal *Salmonella* isolates collected in the United States in 2011, 0.2% were ciprofloxacin resistant (369).

The development of nontyphoidal *Salmonella* isolates resistant to extended-spectrum cephalosporins, such as ceftriaxone, represents another substantial public health concern. These drugs are important for treating invasive *Salmonella* infections, especially among children, among whom fluoroquinolones may be avoided. Resistance to extended-spectrum cephalosporins has been recognized in nontyphoidal *Salmonella* since the mid-1980s and is commonly mediated through  $\beta$ -lactamases of the ESBL or AmpC type. Some of the earliest reports on cephalosporin-resistant isolates of nontyphoidal *Salmonella* originated in North Africa. During 1984 and 1990, cephalosporin-resistant strains were frequently isolated in pediatric units of Tunisian hospitals (375, 376). In Southeast Asia, cephalosporin resistance has been reported from Singapore, the Philippines, and Thailand (373, 377). In Thailand, isolates harboring enzymes of the CMY and CTX-M types have been described (378, 379). Importantly, some of the cephalosporin-resistant nontyphoidal *Salmonella* isolates in Thailand also show resistance to fluoroquinolones (379–381). Such infections might require the use of more expensive drugs such as carbapenems or tigecycline.

In Europe, cephalosporin-resistant nontyphoidal *Salmonella* was first detected in France and Italy in 1989 and 1990, respectively (382, 383). A CTX-M-producing clone of *Salmonella* serovar Typhimurium spread in Russia, Hungary, and Greece between 1996 and 1999, and sporadic cases and outbreaks involving CMY-producing *Salmonella* serovar Newport were reported from France between 2000 and 2005 (375, 384).

In North America, reports on  $\beta$ -lactamase-producing isolates

of nontyphoidal *Salmonella* started to appear in the mid-1990s. In the United States, a national survey of 4,003 *Salmonella* isolates collected in 1995 found 3 (<0.1%) ceftriaxone-resistant isolates, each of which had been acquired outside the United States (385). Early reports of ceftriaxone-resistant nontyphoidal *Salmonella* appeared in the mid- to late 1990s (386). The first ESBL-producing strain detected in Canada was an SHV-producing *Salmonella* serovar Typhimurium strain identified in 2000 (387). Two years later, the first CMY-producing *Salmonella* strain was reported during a small outbreak of *Salmonella* serovar Newport in Alberta, Canada (388). Since then, multiple studies have reported on the occurrence of CMY and ESBL enzymes among *Salmonella* isolates collected from human, animal, and retail meat sources in Canada and the United States (389–399). Perhaps the most notable trend in the United States has been the emergence of MDR *Salmonella* serovar Newport with an AmpC phenotype (400). These strains emerged in the early 2000s and harbored plasmids encoding cephalosporin resistance (*bla*<sub>CMY</sub>) and the R-type ACSSuT phenotype (400). According to NARMS, the proportion of *Salmonella* serovar Newport isolates with this phenotype peaked at 25% in 2001 but had declined to 13% by 2005. More recently ceftriaxone-resistant *Salmonella* serovar Heidelberg has emerged in the United States (390, 401).

Over recent years, several reports have documented the emergence of extensively drug-resistant isolates of nontyphoidal *Salmonella*. *Salmonella* serovar Typhimurium isolates resistant to 12 to 15 antimicrobial agents, comprising 6 or 7 CLSI drug classes, including cepheims, have been reported from Malaysia and Vietnam (402–404). Similarly, *Salmonella* isolates resistant to 6 or 7 antimicrobial agents, comprising 3 to 5 CLSI drug classes, have been detected in Thailand (374). A recent trend is the development of extensively drug-resistant isolates of *Salmonella* serovar Kentucky. A ciprofloxacin-resistant strain of *Salmonella* serovar Kentucky (ST198-X1) that originally emerged in Egypt and spread throughout Africa and the Middle East from 2002 to 2008 has now acquired additional resistance (405). Since 2009, variants displaying resistance to extended-spectrum cephalosporins and carbapenems have been detected. Nontyphoidal *Salmonella* isolates displaying carbapenem resistance have been reported from multiple countries, including China, Columbia, Pakistan, and the United States. Among these isolates, *Klebsiella pneumoniae* carbapenemase and New Delhi metallo-beta-lactamase-1 enzymes were most prevalent (406–410). Of concern is that some of these isolates are also resistant to most aminoglycosides, trimethoprim-sulfamethoxazole, and azithromycin (405).

### Molecular Mechanisms of Resistance

**Multiple-drug resistance.** Among typhoidal *Salmonella* isolates, resistance to the traditional first-line antimicrobials ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole is commonly caused by resistance determinants located on plasmids. Resistance to ampicillin is often mediated through  $\beta$ -lactamases (e.g., *bla*<sub>PSE</sub> and *bla*<sub>TEM</sub>), whereas several mechanisms may be associated with chloramphenicol resistance. Three types of chloramphenicol acetyltransferases (CATs) (types I to III) have been described in Gram-negative bacteria, but resistance due to the production of CAT of type I has been encountered most frequently in *Enterobacteriaceae* (411). Genes involving nonenzymatic resistance mechanisms, such as *cmlA* and *floR*, have also been found in *Salmonella enterica* (411, 412). Both trimethoprim

and sulfamethoxazole are folate pathway inhibitors that prevent the synthesis of DNA. Resistance to both drugs occurs by acquisition of genes encoding folate pathway enzymes that do not bind these compounds. In *Salmonella enterica*, resistance to trimethoprim is mediated through various dihydrofolate reductase (*dhfr*) genes, whereas sulfamethoxazole resistance is due to the presence of *sul* genes such as *sul1* or *sul2* (412).

The genes mediating R-type ACSSuT in nontyphoidal *Salmonella* are commonly clustered together in a chromosomal genetic element called *Salmonella* genomic island 1 (SGI-1). This element was first identified in *Salmonella* serovar Typhimurium DT104 but has since then been detected in many other serovars, including *Salmonella* serovars Agona, Albany, Cerro, Derby, Dusseldorf, Emek, Haifa, Infantis, Kentucky, Kiambu, Kingston, Meleagridis, Newport, Paratyphi B, and Tallahassee (413–415). In the classic SGI-1, a 14-kb region bracketed by two integron structures within this chromosomal element contains the antimicrobial resistance genes contributing to its ACSSuT properties: *bla*<sub>PSE-1</sub> conferring resistance to ampicillin, *floR* to chloramphenicol and florfenicol, *aadA2* to streptomycin, *sul1* to sulfonamides, and *tetG* to tetracycline (416).

**Fluoroquinolone resistance.** Fluoroquinolones target the two enzymes DNA gyrase and topoisomerase IV, whose subunits are encoded by the *gyrA* and *gyrB* and the *parC* and *parE* genes (417). Mutations in the quinolone resistance-determining regions (QRDRs) of these genes may confer reduced susceptibility or resistance to fluoroquinolones, depending on the number of mutations acquired (417, 418). A single point mutation in the *gyrA* gene, typically Ser-83 to Phe, Ser-83 to Tyr, Asp-87 to Asn, or Asp-87 to Gly, will confer resistance to the quinolone nalidixic acid and decreased susceptibility to ciprofloxacin. Two or more mutations in the *gyrA* gene or other topoisomerase genes are required to confer full clinical resistance to ciprofloxacin (MIC,  $\geq 1$   $\mu\text{g/ml}$ ) (418–421).

In addition to the chromosomally encoded mechanisms, plasmid-mediated resistance mechanisms have been described. The first plasmid-mediated quinolone resistance (PMQR) mechanism, *qnrA*, was described in the late 1990s, and since then, a variety of other plasmid-mediated mechanisms have been discovered in *Enterobacteriaceae*, including different *qnr* variants, *aac(6′)-Ib-cr*, *qepA*, and *oqxAB* (422, 423). Among nontyphoidal *Salmonella* strains, a number of *qnr* variants and the *aac(6′)-Ib-cr* mechanism have been detected (424). Reports on PMQR mechanisms among typhoidal *Salmonella* isolates are rare but include a *qnrB2*-producing isolate detected in Germany and three *qnrS1*-producing isolates detected in the United States (364, 425). The plasmid-mediated mechanisms typically confer decreased susceptibility to ciprofloxacin in the MIC range of 0.125 to 1.0  $\mu\text{g/ml}$  and a modest increase in susceptibility to nalidixic acid in the MIC range of 8 to 32  $\mu\text{g/ml}$  (422, 426, 427).

**Cephalosporin resistance.** Cephalosporins belong to the group of  $\beta$ -lactam antimicrobials and disrupt the bacterial cell wall synthesis by targeting penicillin binding proteins (PBPs) and the cross-linking of the peptidoglycan (428). Resistance to cephalosporins, including extended-spectrum cephalosporins such as ceftriaxone, is commonly mediated through  $\beta$ -lactamases that inactivate the drug by cleaving the  $\beta$ -lactam ring. The  $\beta$ -lactamases mediating resistance to extended-spectrum cephalosporins can be divided into three groups: extended-spectrum  $\beta$ -lactamases (ESBLs), carbapenemases, and AmpC-type  $\beta$ -lactamases (429,

430). Among the AmpC plasmid-mediated  $\beta$ -lactamases, cephamycinases (CMY), encoded by *bla*<sub>CMY</sub> genes, are the predominant cause of cephalosporin resistance in nontyphoidal *Salmonella*. The genes encoding the  $\beta$ -lactamase enzymes are commonly located on mobile genetic elements such as plasmids, transposons, and integrons. Consequently, resistance may spread horizontally between isolates, clones, and serovars.

**Macrolide resistance.** Macrolides inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome. Resistance mechanisms have been detected in *Salmonella enterica* isolates with elevated azithromycin MICs, here defined as MICs of >16  $\mu$ g/ml. Among nontyphoidal *Salmonella* isolates, a macrolide-2'-phosphotransferase encoded by the *mphA* gene has been described (405, 431). The first case of azithromycin treatment failure in a patient with invasive *Salmonella* infection was reported in 2010 (432). This infection was due to a *Salmonella* serovar Paratyphi A isolate displaying an azithromycin MIC of 256  $\mu$ g/ml (432).

### ANTIMICROBIAL MANAGEMENT

The aims of management of invasive *Salmonella* infections are to resolve clinical symptoms by eliminating the infection with antimicrobials, to provide supportive treatment with fluids and nutrition, and to monitor for the development of complications. Effective antimicrobial therapy reduces mortality and complications and shortens the illness. In enteric fever, antimicrobial treatment may eradicate fecal carriage and reduce onward transmission. In areas of endemicity, antimicrobial treatment for typhoid fever is often started empirically based on the syndrome of fever for 3 to 4 days or more, constitutional symptoms (e.g., malaise and fatigue), symptoms or signs in the gastrointestinal system, a negative malaria smear, and no other clear source of infection. Antimicrobial agents are not recommended for treatment of nonsevere, nontyphoidal *Salmonella* diarrhea in healthy adults or children, but they are recommended for people with evidence of sepsis or extraintestinal infection or for specific populations at risk for bacteremia and disseminated disease.

Enteric fever is an intracellular infection involving the reticuloendothelial system, particularly bone marrow, liver, and spleen (52). Invasive nontyphoidal *Salmonella* has also been shown to establish an intracellular niche in the blood and bone marrow (162). Therefore, effective treatment depends on the ability of antimicrobials to penetrate intracellular sites of infection in the reticuloendothelial system and gallbladder. Some antimicrobials, including gentamicin and first- and second-generation cephalosporins such as cefuroxime, appear to be effective *in vitro* but are ineffective *in vivo* and should not be used in enteric fever (433).

### Traditional First-Line Antimicrobials

Chloramphenicol was the first antimicrobial found to be effective in enteric fever and for many years was the standard treatment (315). Treatment with chloramphenicol led to symptom resolution within 4 to 6 days and transformed a prolonged, debilitating, and potentially fatal disease into a treatable condition with a low case fatality ratio. A physician using chloramphenicol to treat typhoid fever for the first time commented: "... the clinical improvement and complete transformation in a few days can only be appreciated by clinicians who have had previous experience of typhoid fever and have known their own helplessness in the past to affect its protracted course. . . its great value in saving life and

curtailing morbidity in this disease is incontestable" (434). Oral chloramphenicol treatment results in serum concentrations between 5 and 20  $\mu$ g/ml above the usual wild-type MIC (435). The succinate ester prodrug is used for intravenous or intramuscular administration and gives lower serum levels than the oral form (436, 437). Chloramphenicol has been shown to be clinically effective in a number of studies (341, 438–447). Disadvantages of chloramphenicol are its four-times-daily administration and the need to give it for at least 2 weeks to reduce the 10 to 15% risk of relapse. Dose-related and reversible bone marrow depression and irreversible bone marrow aplasia that is rare, unpredictable, and often fatal may occur (448). Amoxicillin and trimethoprim-sulfamethoxazole were shown to have efficacy generally comparable to that of chloramphenicol with less risk of toxicity, although they also needed to be given for at least 2 weeks to avoid relapse (439, 449–456). The experience with amoxicillin was less convincing (456–458). Chloramphenicol, amoxicillin, and trimethoprim-sulfamethoxazole were widely available and affordable in areas of endemicity and remained the standard of care for many years. The emergence and spread of MDR strains of *Salmonella* serovars Typhi and Paratyphi A led to the evaluation of new antimicrobials. The extended-spectrum cephalosporins, fluoroquinolones, and azithromycin were established as effective alternatives.

### Fluoroquinolones

The fluoroquinolones, in particular ciprofloxacin and ofloxacin but also including fleroxacin and pefloxacin, were evaluated for enteric fever treatment as the MDR strains emerged. Peak plasma levels of ciprofloxacin and ofloxacin after oral administration were initially well above the prevailing MICs of infecting strains (481–483). The drugs were concentrated intracellularly at the site of infection (484, 485) and were rapidly bactericidal *in vitro* (481, 486). When given for duration of 7 to 14 days, fluoroquinolones were often 100% effective with very low levels of relapse (329, 342, 443, 470, 487–505). The clinical response was rapid, with fever resolution within 3 to 5 days. A number of studies were conducted, predominantly in Vietnam, with a shorter course of treatment of 5 days (506, 507) or 2 or 3 days (507–510) in uncomplicated disease with broadly similar results. Fleroxacin and pefloxacin were equally effective, although norfloxacin is not recommended because of low tissue concentrations. As these fluoroquinolones could conveniently be given orally and local generically produced drugs were relatively affordable, they became widely used for treating suspected and confirmed cases of enteric fever.

For invasive nontyphoidal *Salmonella* there is only very limited historical experience of the use of chloramphenicol compared to ciprofloxacin. Ciprofloxacin was introduced following the emergence of resistance to chloramphenicol (114) in treatment of invasive nontyphoidal *Salmonella* in Africa. The reported recurrence ratio after treatment with chloramphenicol was 43% (154), compared to 30% following treatment with ciprofloxacin (162). This difference might be attributable to improved intracellular penetration of the fluoroquinolone. The case fatality ratio also fell gradually over the reported period, but this could be attributable to multiple effects other than the change in antimicrobial use (114).

Over time, physicians in areas of endemicity and those treating returning travelers began to report cases of fluoroquinolone failure when treating enteric fever despite the laboratory reporting a



susceptible isolate (343, 419, 511–519). It became clear that a subset of strains of *Salmonella* serovars Typhi and Paratyphi A had emerged that were less susceptible to the fluoroquinolones. They showed decreased susceptibility to ciprofloxacin (MICs of 0.125 to 0.5  $\mu\text{g/ml}$ , compared with the wild-type MIC of  $\leq 0.03 \mu\text{g/ml}$ ), and the decreased susceptibility is most commonly mediated by point mutations in genes encoding DNA gyrase, the target enzyme for the drug (486, 513, 514, 520–522). Isolates that have this decreased-susceptibility phenotype were not defined as resistant by the existing ciprofloxacin interpretive criteria for disk diffusion but were usually found to be nalidixic acid resistant. Nalidixic acid resistance has proved to be a useful, although not a completely accurate, laboratory marker of decreased fluoroquinolone susceptibility (337). The accumulating evidence that these strains are associated with an impaired response to ciprofloxacin and ofloxacin has led to a recent revision of the Clinical and Laboratory Standards Institute (CLSI) breakpoint guidelines such that they are now classified as intermediate (523, 524). Ciprofloxacin-intermediate strains have become common in Asia, sometime causing large outbreaks, with reports also in sub-Saharan Africa, and South America (486, 525–529). Studies with whole-genome sequencing of global *Salmonella* serovar Typhi collections have shown that a particular haplotype, H58, is more likely to be MDR and to have intermediate susceptibility to ciprofloxacin (530, 531). This haplotype has become dominant in many regions and may have a competitive advantage compared with other haplotypes (532–536).

Infection with *Salmonella enterica* isolates with intermediate susceptibility to ciprofloxacin may respond to higher doses or longer durations of treatment with ciprofloxacin or ofloxacin; failure does not occur in all cases (537). However, even if fluoroquinolone treatment of such infections is successful, higher levels of fecal shedding posttreatment may occur, driving further transmission of strains (520). Where possible, fluoroquinolones should be avoided in patients infected with strains with intermediate susceptibility to fluoroquinolones. Alternatives include extended-spectrum cephalosporins (e.g., ceftriaxone) and, in nonsevere cases, azithromycin or the traditional first-line antimicrobials, if susceptible. If fluoroquinolones are the only available option, for example, in outpatient management, they should be used at the maximum dose, such as 20 mg/kg/day of ciprofloxacin, for at least 7 days.

The later-generation fluoroquinolone gatifloxacin has been found to be an effective alternative for *Salmonella* infections with isolates with intermediate ciprofloxacin susceptibility. A single daily dose of 10 mg/kg for 7 days has achieved cure in more than 90% of patients and short fever clearance times (341, 480, 537, 538). Gatifloxacin targets both DNA gyrase and topoisomerase IV. Therefore, gatifloxacin is less inhibited by the common mutations of the *gyrA* gene of *Salmonella* serovar Typhi than are ciprofloxacin and ofloxacin (486). Fully fluoroquinolone-resistant *Salmonella* isolates with a ciprofloxacin MIC of  $\geq 1 \mu\text{g/ml}$  are unlikely to respond to any of the fluoroquinolones. Such isolates are increasing in South Asia and are sporadically reported from other countries (350–352, 539–543).

There are some patient safety concerns with the fluoroquinolones. A caution with children is the potential for damage to growing weight-bearing joints and cartilage, based on studies in immature animals. The available evidence in humans suggests that if used in short courses the risk of an effect on growth and joint develop-

ment is low and that musculo-skeletal side effects are reversible (544–551). In most countries the use of fluoroquinolones in children is relatively contraindicated except for use in multidrug-resistant infections where there are no suitable alternative. The fluoroquinolones do carry a risk of tendon damage in patients over 60 years of age, those on concomitant corticosteroids, or those with a history of tendon disorders. Dysglycemia among the elderly and those with diabetes has been reported with gatifloxacin, leading to the withdrawal of the drug from the American and other markets (552). Careful monitoring of glucose levels in patients recruited to typhoid studies in Nepal have not shown adverse effects, and most typhoid fever cases in areas of endemicity occur in children and young adults rather than the elderly (341). While it is uncommon for patients with typhoid fever to have diabetes in areas of endemicity, diabetes is an emerging problem among adults in South Asia. Gatifloxacin should be avoided in patients over 50 years of age and in those with diabetes or renal failure.

### Extended-Spectrum Cephalosporins

Ceftriaxone has been the principal cephalosporin evaluated in clinical trials of typhoid fever, although cefotaxime and cefoperazone have also proved effective in a few studies (459, 460). Peak drug levels of ceftriaxone of  $> 140 \mu\text{g/ml}$  and trough levels of  $> 22 \mu\text{g/ml}$  provide unbound concentrations well above a typical MIC of 0.03 to 0.06  $\mu\text{g/ml}$  (461, 462). Ceftriaxone is generally safe to use, including in children, is slowly bactericidal against *Salmonella* serovar Typhi *in vitro*, and is able to penetrate and kill intracellular bacteria (463, 464). Ceftriaxone has been used to treat typhoid in durations of 14 days (465–467), 7 days (342, 468–470), 5 days (440, 471–473), and 3 days (442, 474, 475). The proportion of patients cured has varied from 70% to more than 90%. The resolution of symptoms is invariably slow, often with the fever clearance times of 6 to 8 days. Relapse may occur in more than 10% of patients in some studies, particularly when the duration of treatment is 7 days or less. The optimum duration of treatment is unclear. While the cost and inconvenience of parenteral administration of ceftriaxone are disadvantages, once-daily administration makes this easier. Oral extended-spectrum cephalosporins such as cefixime have also been studied. Although early results were promising (465, 472, 476–478), in two later studies the treatment response was slow and clinical failures and relapses were seen (479, 480).

### Azithromycin

Azithromycin is increasingly being used for empiric treatment of uncomplicated enteric fever, especially in areas where MDR and fluoroquinolone-resistant infections are prevalent (444, 469, 501, 511, 516). The MICs of strains are usually in the range of 0.25 to 16  $\mu\text{g/ml}$  (553–556). Serum levels after oral administration are 0.04 to 0.4  $\mu\text{g/ml}$  (557). Azithromycin shows excellent penetration into most tissues and achieves intracellular concentrations inside macrophages and neutrophils that are 10 to 100 times greater than serum concentrations, with slow release from this intracellular site (558, 559). The drug has a long half-life of 2 to 3 days, allowing once-daily administration, and is safe to use in children. The immunomodulatory effects of azithromycin may also be important by reversing the immunoparalysis seen in typhoid (28, 29, 560). Although some initial clinical studies were disappointing (561), subsequent randomized controlled trials have confirmed azithromycin to be equivalent or superior to chloramphenicol, fluoro-

quinolones, and extended-spectrum cephalosporins for the management of uncomplicated typhoid fever and associated with a prompt resolution of clinical symptoms and low prevalence of relapse and convalescent fecal carriage (444, 469, 473, 501, 511, 516, 538). Doses have varied between 10 and 20 mg/kg/day for between 5 and 7 days, and the optimum dose and duration are yet to be determined. Occasional patients in these studies have demonstrated a slow clearance of bacteremia. Several studies have reported azithromycin MIC distributions for typhoidal and nontyphoidal *Salmonella* strains (501, 511, 562–565). These studies have led to a suggested epidemiologic MIC cutoff value of  $\leq 16$   $\mu\text{g/ml}$  for wild-type strains (566, 567). Clinical interpretive criteria for disk diffusion and MIC testing have recently been adopted by CLSI for *Salmonella* serovar Typhi but not yet for *Salmonella* serovar Paratyphi A (570). There are sporadic reports of strains with an azithromycin MIC of  $\geq 32$   $\mu\text{g/ml}$  but limited published data on the clinical response to azithromycin in such infections (432, 562, 563, 568, 569). The newly established CLSI guidelines for azithromycin disk diffusion and MIC interpretive criteria for *Salmonella* serovar Typhi were published in CLSI document M100 in 2015 (570).

### Carbapenems and Tigecycline

If combined resistance to all first- and second-line drugs develops, the carbapenems (e.g., imipenem, meropenem, and ertapenem), and tigecycline could be potential alternatives (571). There are few reports describing the use of these potentially expensive drugs (572). In many areas of South Asia, increasing proportions of *Salmonella* isolates have regained susceptibility to the traditional first-line drugs chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. These older drugs could be used again, although the prevalence of MDR *Salmonella* may rise again.

### Antimicrobial Combinations

Combinations of fluoroquinolones, cephalosporins, and azithromycin are probably used quite frequently, particularly in patients who fail to respond promptly (517, 573). The potential advantages of antimicrobial combinations include a broadening of the spectrum of antimicrobial activity, particularly in the face of potential drug-resistant strains, utilization of any potential synergy between the drugs, and the potential to reduce the emergence of resistant strains during the course of treatment. However, there are few studies of the *in vitro* interactions between antimicrobials for *Salmonella* isolates (574, 575).

### Pregnancy

Ampicillin, amoxicillin, and ceftriaxone are considered safe in pregnant women with enteric fever (63, 576). Fluoroquinolones have been occasionally used in pregnant patients infected with MDR *Salmonella* isolates (577, 578). Animal studies of azithromycin have not revealed evidence of fetotoxicity, although there are only limited controlled data in human pregnancy (579). The U.S. Food and Drug Administration has assigned azithromycin to pregnancy category B, indicating that it should be given during pregnancy only when benefit outweighs risk. Azithromycin is excreted into human milk, and the manufacturer recommends that caution be used when administering azithromycin to nursing women.

### Treatment of Severe Disease

Gastrointestinal bleeding is usually self-limiting, and few patients require a blood transfusion. In exceptional circumstances, surgery, intra-arterial vasopressin, or colonoscopic interventions have been used to halt hemorrhage (580–582). The management of intestinal perforation includes nasogastric suction, administration of fluids to correct hypotension, and prompt surgery. Surgery has been demonstrated to lead to improved survival compared with a conservative approach (73). The survival of patients undergoing surgery for perforation is generally 70 to 75% but reaches 97% in the best series (72–74). In contrast, approximately 30% of conservatively managed patients survive. Simple closure of perforations is usually adequate, although procedures to bypass severely affected sections of the ileum are sometimes used. Closure of perforations should be accompanied by vigorous peritoneal toilet. Metronidazole or clindamycin should be added to the therapy of ceftriaxone- or fluoroquinolone-treated patients. Metronidazole and aminoglycosides are recommended for patients receiving chloramphenicol, ampicillin, or trimethoprim-sulfamethoxazole.

Enteric fever patients with altered consciousness and hemodynamic shock have high case fatality ratios. A study in Jakarta showed that high doses of dexamethasone substantially reduced the mortality of such severe cases. The criterion for entry to the study was marked mental confusion or shock. Among adults treated with chloramphenicol, dexamethasone at 3 mg/kg infused intravenously over half an hour, followed by eight doses of 1 mg/kg every 6 h, resulted in a 10% case fatality ratio, compared to 55.6% among controls (76). A study using historical controls demonstrated a comparable benefit in children (77). Whether lower doses of glucocorticosteroids would have a similar effect is unclear. A nonrandomized study in Papua New Guinea using lower equivalent doses of hydrocortisone failed to replicate this result (78). It is also unclear whether enteric fever caused by susceptible typhoidal *Salmonella* treated with a second-line antimicrobial agent such as ceftriaxone or a fluoroquinolone would achieve a similar result. It has proved difficult to replicate this study because the number of severe typhoid patients has decreased, possibly because of the ready availability of over-the-counter antimicrobials.

### Treatment of Chronic Carriage

Eradication of chronic carriage has been achieved with longer durations of antimicrobial therapy than are required for management of acute infection. The choice of antimicrobial depends on the susceptibility of the strain. Ampicillin or amoxicillin, sometimes combined with probenecid, trimethoprim-sulfamethoxazole, and fluoroquinolones have been used with some success (583–591). Cholecystectomy can be considered if antimicrobials fail, but the surgery can carry risks, and there should be additional indications for operation. The success of surgery for the elimination of chronic carriage is increased by giving antimicrobials at the same time (592).

### Evidence Needs for Antimicrobial Management

Most physicians base their therapeutic choices on international or country guidelines, when available, or expert opinion (593–596). Experience based on routine practice may be unreliable. In low-resource areas, the diagnosis of invasive *Salmonella* infection is usually unconfirmed, and patients treated as outpatients who do

not improve or subsequently relapse may return to a different health care facility. Antimicrobials are easily available without prescription in pharmacies and shops in most developing countries, and counterfeit or substandard antimicrobials are likely to be common (597). The detection and management of convalescent and chronic carriage are of crucial public health importance, particularly in the light of widespread drug resistance, but have received little attention.

The evidence base of randomized controlled trials to guide enteric fever treatment is limited and particularly so for invasive nontyphoidal salmonellosis. Many randomized trials have been small and underpowered to demonstrate significant differences between antimicrobial choices. Systematic reviews of the evidence from existing studies are useful (505, 598). Further well-conducted randomized clinical trials, with detailed microbiology and accompanying pharmacokinetic and pharmacodynamic analysis, are essential to define safe and effective regimens for patients. Such trials are likely to require multicenter designs to be able to recruit sufficient patients over a reasonable period of time.

The appropriate timing of and early and late outcomes following antiretroviral therapy in patients presenting with invasive NTS are almost entirely unknown. This is an area where further study and practical recommendations would be useful.

## CONCLUSIONS

*Salmonella enterica* infections are common causes of bloodstream infection in low-resource areas, where they may be difficult to distinguish from other febrile illnesses and may be associated with a high case fatality ratio. Microbiologic culture of blood or bone marrow remains the mainstay of laboratory diagnosis. Antimicrobial resistance has emerged in *Salmonella enterica*, initially to the traditional first-line drugs chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. Decreased fluoroquinolone susceptibility and then fluoroquinolone resistance have developed in association with chromosomal mutations in the quinolone resistance-determining regions of genes encoding DNA gyrase and topoisomerase IV and also by plasmid-mediated resistance mechanisms. In 2013, CLSI lowered the ciprofloxacin susceptibility breakpoints to account for accumulating clinical, microbiologic, and pharmacokinetic-pharmacodynamic data suggesting that revision was needed for contemporary invasive *Salmonella* infections (523). Resistance to extended-spectrum cephalosporins has occurred more often in nontyphoidal than in typhoidal *Salmonella* strains. Azithromycin is effective for the management of uncomplicated typhoid fever and may serve as an alternative oral drug in areas where fluoroquinolone resistance is common. Newly established CLSI guidelines for azithromycin disk diffusion and MIC interpretive criteria for *Salmonella* serovar Typhi were published in CLSI document M100 in 2015 (570).

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