of the Peyer's patches, which may be mediated by bacterial products that promote cell death as well as the inflammatory response.

In contrast to enteric fever, which is characterized by an infiltration of mononuclear cells into the small-bowel mucosa, NTS gastroenteritis is characterized by massive polymorphonuclear leukocyte infiltration into both the large- and small-bowel mucosa. This response appears to depend on the induction of interleukin 8, a strong neutrophil chemotactic factor, which is secreted by intestinal cells as a result of *Salmonella* colonization and translocation of bacterial proteins into host cell cytoplasm. The degranulation and release of toxic substances by neutrophils may result in damage to the intestinal mucosa, causing the inflammatory diarrhea observed with nontyphoidal gastroenteritis. An additional important factor in the persistence of nontyphoidal salmonellae in the intestinal tract and the organisms' capacity to compete with endogenous flora is the ability to utilize the sulfur-containing compound tetrathionate for metabolism in a microaerophilic environment. In the presence of intestinal inflammation, tetrathionate is generated from thiosulfate produced by epithelial cells through inflammatory cell production of reactive oxygen species.

ENTERIC (TYPHOID) FEVER

Enteric (typhoid) fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S. typhi* or *S. paratyphi*. The disease was initially called *typhoid fever* because of its clinical similarity to typhus. In the early 1800s, typhoid fever was clearly defined pathologically as a unique illness on the basis of its association with enlarged Peyer's patches and mesenteric lymph nodes. In 1869, given the anatomic site of infection, the term *enteric fever* was proposed as an alternative designation to distinguish typhoid fever from typhus. However, to this day, the two designations are used interchangeably.

EPIDEMIOLOGY

In contrast to other *Salmonella* serotypes, the etiologic agents of enteric fever—*S. typhi* and *S. paratyphi* serotypes A, B, and C—have no known hosts other than humans. Most commonly, food-borne or waterborne transmission results from fecal contamination by ill or asymptomatic chronic carriers. Sexual transmission between male partners has been described. Health care workers occasionally acquire enteric fever after exposure to infected patients or during processing of clinical specimens and cultures.

With improvements in food handling and water/sewage treatment, enteric fever has become rare in developed nations. Worldwide, however, there are an estimated 27 million cases of enteric fever, with 200,000–600,000 deaths annually. The annual incidence is highest (>100 cases/100,000 population) in south-central and Southeast Asia; medium (10–100 cases/100,000) in the rest of Asia, Africa, Latin America, and Oceania (excluding Australia and New Zealand); and low in other parts of the world (Fig. 190-1). A high incidence of enteric fever correlates with poor sanitation and lack of access to clean drinking water. In endemic regions, enteric fever is more common in urban than rural areas and among young children and adolescents than among other age groups. Risk factors include contaminated water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilized with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior *Helicobacter pylori* infection (an association probably related to chronically reduced gastric acidity). It is estimated that there is one case of paratyphoid fever for every four cases of typhoid fever, but the incidence of infection associated with *S. paratyphi* A appears to be increasing, especially in India; this increase may be a result of vaccination for *S. typhi*.

Multidrug-resistant (MDR) strains of *S. typhi* emerged in the 1980s in China and Southeast Asia and have since disseminated widely. These strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim—antibiotics long used to treat enteric fever. With the increased use of fluoroquinolones to treat MDR enteric fever in the 1990s, strains of *S. typhi* and *S. paratyphi* with decreased ciprofloxacin susceptibility (DCS; minimal inhibitory concentration [MIC], 0.125–0.5 μg/mL) or ciprofloxacin resistance (MIC, ≥1 μg/mL) have emerged on the Indian subcontinent, in southern Asia, and (most recently) in sub-Saharan Africa and have been associated with clinical treatment failure. Testing of isolates for resistance to the first-generation quinolone nalidixic acid detects many but not all strains with reduced susceptibility to ciprofloxacin and is no longer recommended. Strains of *S. typhi* and *S. paratyphi* producing extended-spectrum β-lactamases have emerged recently, primarily in India and Nepal.

Approximately 300 cases of typhoid and 150 cases of paratyphoid fever are reported annually in the United States. Of 1902 cases of *S. typhi*–associated enteric fever reported to the Centers for Disease Control and Prevention in 1999–2006, 79% were associated with recent international travel, most commonly to India (47%), Pakistan (10%), Bangladesh (10%), Mexico (7%), and the Philippines (4%). Only 5% of travelers diagnosed with enteric fever had received *S. typhi* vaccine. Overall, 13% of *S. typhi* isolates in the United States were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX), and the proportion of DCS isolates increased from 19% in 1999 to 58% in 2006. Infection with DCS *S. typhi* was associated with travel to the Indian subcontinent. Of the 25–30% of reported cases of enteric fever in the United States that are domestically acquired, the majority are sporadic, but outbreaks linked to contaminated food products and previously unrecognized chronic carriers continue to occur.

CLINICAL COURSE

Enteric fever is a misnomer, in that the hallmark features of this disease—fever and abdominal pain—are variable. While fever is documented at presentation in >75% of cases, abdominal pain is reported in only 30–40%. Thus, a high index of suspicion for this potentially fatal systemic illness is necessary when a person presents with fever and a history of recent travel to a developing country.

The incubation period for *S. typhi* averages 10–14 days but ranges from 5 to 21 days, depending on the inoculum size and the host's health and immune status. The most prominent symptom is prolonged fever (38.8°–40.5°C; 101.8°–104.9°F), which can continue for

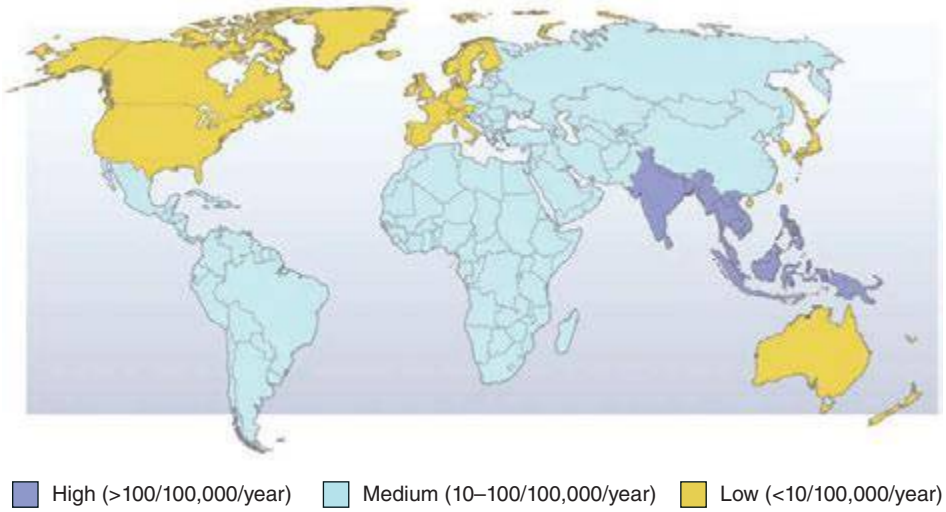

FIGURE 190-1 Annual incidence of typhoid fever per 100,000 population. *(Adapted from JA Crump et al: The global burden of typhoid fever. Bull World Health Organ 82:346, 2004.)*