Typhoid Fever: Recent Advances in Understanding, Diagnosis, and Management Strategies for Endemic Regions

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Abstract

Typhoid fever, caused by *Salmonella enterica* serotype Typhi, remains a significant public health challenge in developing countries despite major declines in incidence in the Western world. Historically, typhoid fever was a major cause of morbidity and mortality in Europe and the United States, primarily due to poor sanitation and inadequate water supply. Advances in public health infrastructure have markedly reduced its prevalence in developed regions, but it continues to affect millions annually in parts of Asia, including Bangladesh. The disease disproportionately impacts children and persists in areas with suboptimal sanitation and overcrowded living conditions. In Bangladesh, inadequate data on typhoid fever burden complicates effective management and control. Challenges include the prevalence of outpatients, insufficient diagnostic facilities, unreliable record-keeping, and limitations of the Widal test, which has moderate sensitivity and specificity. This review aims to consolidate recent advancements in understanding typhoid fever, particularly within the Indian context, by examining its epidemiology, pathogenesis, symptomatology, diagnostic methods, and treatment strategies. Notable epidemiological trends reveal high incidence rates in South Asia, with significant seasonal variation. Improved diagnostic tools, such as PCR and newer serological tests, are emerging, but blood culture remains the gold standard. Treatment has evolved with concerns over drug resistance, and prevention strategies emphasize the importance of improved sanitation and water safety. This review highlights the need for enhanced public health efforts and research to address the persistent challenges of typhoid fever in endemic regions.

Keywords: Typhoid Fever, *Salmonella Typhi*, Epidemiology, Diagnostic Methods, Antimicrobial Resistance.

Significance | Understanding typhoid fever's modern challenges is crucial for improving diagnosis, treatment, and prevention, especially in endemic regions.

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Introduction

Typhoid fever, a serious and potentially fatal bacterial infection, was once a leading cause of morbidity and mortality in the Western world. Two centuries ago, the burden of typhoid, also known as enteric fever, was a major public health challenge in Europe and the United States (Lynch, M. F. et al., 2009). The disease, caused by the bacterium *Salmonella enterica* serotype Typhi, led to widespread suffering and death, particularly in densely populated urban areas where sanitation was poor and access to clean water was limited (Crump, J.A., et al., 2004). However, significant improvements in sanitation, hygiene, and public health infrastructure over the past two centuries have dramatically reduced the incidence of typhoid fever in these regions. Today, typhoid fever is rare in developed countries, with only sporadic cases reported, primarily among

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travellers returning from endemic regions (Stuart, B.M. et al., 1946). Despite the progress made in controlling typhoid fever in the Western world, the disease remains a significant public health concern in many developing countries, including Bangladesh. In these regions, typhoid fever continues to pose a serious threat to public health, particularly among vulnerable populations such as children (EDELMAN, R., et al., 1986). The paediatric population is disproportionately affected by typhoid fever, but the disease also remains an important cause of morbidity and mortality among adults. In countries like Bangladesh, the combination of inadequate sanitation, limited access to clean water, and overcrowded living conditions creates an environment in which typhoid fever can thrive. The disease's persistence in these regions underscores the need for continued efforts to improve public health infrastructure and to develop effective strategies for prevention, diagnosis, and treatment (NAP., 1986).

In Bangladesh, the situation is particularly concerning due to the lack of reliable data on the true burden of typhoid fever. Several factors contribute to this data gap. First, many patients with fever are treated as outpatients, and thus, their cases may go unrecorded in hospital databases. Second, hospitals in rural areas, which represent a significant portion of the country, often lack the necessary facilities for blood culture, the gold standard for diagnosing typhoid fever (Kothari,A. et al., 2008). Third, many health clinics and hospitals do not maintain proper records, making it difficult to track the incidence and prevalence of the disease. Additionally, the Widal test, which is commonly used in Bangladesh for diagnosing typhoid fever, has significant limitations in terms of sensitivity and specificity, leading to both false positives and negatives. These challenges make it extremely difficult to obtain reliable data to estimate the burden of typhoid fever in Bangladesh (IHME., 2012). Given these challenges, there is a pressing need for a comprehensive review of the recent advances in our understanding of typhoid fever, particularly in the Indian context. Such a review would not only help to shed light on the current epidemiological trends but also provide insights into the most effective strategies for controlling and eventually eliminating the disease (Hoffman et al., 2012). This review will focus on several key aspects of typhoid fever, including its epidemiology, pathogenesis, clinical manifestations, diagnostic methods, treatment options, and prevention strategies. By synthesizing the latest research findings, this review aims to provide a clearer picture of the current state of typhoid fever in Bangladesh and to identify the most promising avenues for future research and public health interventions.

Epidemiology

In recent years, the epidemiological patterns of typhoid fever and related diseases have undergone significant changes in many developing countries, particularly across Africa, Asia, and Latin America (Gilman et al., 1975). According to recent estimates, over 20 million cases of typhoid fever occur annually in regions with compromised hygiene and sanitation. Notably, Pakistan, India, and Bangladesh collectively account for a staggering 85% of these cases worldwide (Murray, C.J.L et al., 1996).

Children and young adults are disproportionately affected, with studies from Pakistan and Bangladesh indicating that the average age of patients with typhoid fever is around 7 years (Black, R. E ., 1990).Typhoid is also highly seasonal, with 45% of annual cases reported during the monsoon season. In South Asia, the peak incidence typically occurs between July and October, coinciding with the period of heavy rainfall (Levine, M. M. et al., 1987).

Given the burden of this disease, there is a pressing need for standardized epidemiological methods to accurately assess and monitor typhoid incidence (Levine, M.M., 1990). Buckle et al. conducted a comprehensive review, analysing 24 studies that employed blood culture as the diagnostic criterion for typhoid fever. Additionally, five advanced surveillance reports focusing on blood culture confirmed cases were identified, along with a recent publication on the same topic (Klugman et al., 1987).

Collectively, data from these standardized studies span 47 countries across various global regions. Information was also sourced from population-based and prospective vaccine studies in 13 countries (Wahdan et al., 1982). Surveillance systems in developed regions, where systematic national-level monitoring is routine, provided further data. However, paratyphoid fever incidence data were limited, with only nine countries reporting cases. Interestingly, despite its advanced surveillance system, the United States reported no paratyphoid cases during the study period (Crump et al., 2003). Typhoid fever incidence remains high (over 100 cases per 100,000 population annually) in Asia (excluding Japan) and Southern Africa (Srikantiah et al., 2006). In contrast, the incidence is moderate (10-100 cases per 100,000 population) in regions like North Africa, Latin America, the Caribbean, and Oceania. In Europe, North America, Australia, and New Zealand, the incidence is low, with fewer than 10 cases per 100,000 population annually (Brooks et al., 2005). Historical data from Egypt, for example, show a decline in typhoid incidence, from 209 cases per 100,000 in 1972-73 to 48 cases per 100,000 by 1981. More recent research by Crump et al. reports an even lower incidence rate of 13 per 100,000, indicating a significant decline over the years. In developed countries, most cases of typhoid fever occur in travelers, with domestically acquired cases being rare (Crump et al. 2003).

Aetiology

Typhoid fever is a serious infectious disease caused by the bacterium *Salmonella Typhi*. It is primarily transmitted through the oral route, often as a result of ingesting contaminated food or water (Sinha et al., 1990). Due to the bacteria's ability to survive in water for several days, sources such as sewage, freshwater, and groundwater can become significant contributors to the spread of typhoid fever (Chen et al., 2007).

Open defecation is another critical factor in the transmission of the disease, as it can lead to the contamination of nearby water sources. In many developing countries, the practice of consuming cut fruits, such as papaya, that have been left uncovered for extended periods poses a considerable risk (Khan et al., 2006). Papaya, with its neutral pH, can support the growth of various microorganisms, including S. Typhi. A study by Hosoglu et al. in Turkey highlighted that eating cut papaya, lettuce salad, and traditional raw foods like cig köfte are significant contributors to the spread of typhoid fever.

Living in congested areas or households is also associated with an increased risk of contracting typhoid fever. On the other hand, preventive measures such as washing vegetables thoroughly and the consistent use of sanitary latrines have been shown to reduce the risk of infection. A case-control study in Indonesia further identified a link between paratyphoid fever and the consumption of food from street vendors (Ochiai et al 2005).

The overuse of antibiotics has been linked to an increased risk of infection with both drug resistant and drug-sensitive strains of S. Typhi. However, recent studies in Turkey and Bangladesh did not find a direct correlation between antibiotic use and typhoid fever. Prolonged use of antimicrobials can alter the gastrointestinal flora, reducing the body's natural barriers and making it more susceptible to bacterial colonization, including Salmonella (Acharya et al., 1987).

Research by Bhan et al. has revealed a significant association between the presence of serum anti-Helicobacter pylori IgG antibodies and an increased risk of typhoid fever. Genetic factors may also play a role in susceptibility to the disease (Sur et al., 2007). For instance, a study in Vietnam found that specific nucleotide polymorphisms in HLA alleles and the TNF-alpha promoter were linked to a lower risk of typhoid fever. The HLA-DRB1*12 allele, in particular, was associated with protection against complicated forms of the disease.

Bacteriology

Salmonella enterica serovar Typhi is the bacterium responsible for causing typhoid fever. This pathogen is characterized by specific serological markers, including the lipopolysaccharide antigens O9 and O12, the protein flagellar antigen Hd, and the polysaccharide capsular antigen Vi (Sur et al., 2009). The Vi capsular antigen is predominantly associated with *S. enterica* serotype Typhi, though it is also found in some strains of *S. enterica* serotypes Paratyphi C (Hirschfeldii) and Dublin, as well as in Citrobacter freundii. The Vi polysaccharide capsule plays a crucial role in protecting the bacterium against the bactericidal effects of the host's serum, contributing to the pathogen's virulence and ability to evade the immune response (Siddiqui et al., 2006).

Pathogenesis

Typhoid fever, caused by *Salmonella enterica* serotype Typhi, requires an infectious dose of approximately 1000 to 1 million organisms to induce disease in humans. Among the strains of S. Typhi, those positive for the Vi antigen are notably more virulent and infectious compared to Vi-negative strains (Yang et al., 2001).

One of the body's primary defences against S. Typhi is the high acidity of gastric fluid. The acidic environment in the stomach acts as a significant barrier, neutralizing many of the ingested bacteria before they can reach the intestines (Lin et al., 2001). However, conditions that reduce gastric acidity, such as aging, gastrectomy, or the use of proton-pump inhibitors and antacids, can lead to achlorhydria a state of reduced stomach acid thereby increasing susceptibility to typhoid infection.

Once the bacteria pass through the stomach and reach the small intestine, they first adhere to the mucosal cells. Then invade the intestinal mucosa, where they rapidly penetrate the mucosal epithelium either through microfold cells (M cells) or enterocytes (Lin et al., 2000). After crossing the epithelial barrier, *S. Typhi* reaches the lamina propria, a tissue layer beneath the mucosa, where it triggers an influx of macrophages. These immune cells engulf the bacteria but often fail to destroy them. Some of the bacteria remain within the macrophages of the small intestinal lymphoid tissue, while others migrate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes (Simanjuntak et al., 1991). From there, they enter the thoracic duct and eventually the systemic circulation, spreading throughout the body.

The incubation period for typhoid fever is typically between 7 to 14 days. During this time, a complex interaction between the host's immune system and bacterial factors occurs, ultimately leading to the necrosis of Peyer's patches aggregated lymphoid nodules in the small intestine (Vollaard et al., 2005).

In contrast to Asia, where *S. Typhi* is the predominant cause of typhoid fever, non-typhoidal salmonellae, such as *S. Typhimurium,* are often responsible for similar infections in Africa. Despite the difference in causative agents, the clinical manifestations of the disease in these regions are often indistinguishable (Dunn et al., 2005).

Symptomatology

Typhoid fever remains a prevalent febrile illness in developing countries. After an incubation period of 7 to 14 days, the disease typically begins with the onset of fever and general malaise. The fever is often accompanied by chills, headache, anorexia, nausea, vague abdominal discomfort, dry cough, and muscle pain (myalgia) (Lutui et al., 1999). As the disease progresses, symptoms may include a coated tongue, abdominal tenderness, and enlargement of the liver (hepatomegaly) and spleen (splenomegaly).

Advancements in antibiotic treatments have altered the classic presentation of typhoid fever. The once-characteristic slow, stepladder rise in fever and associated toxic symptoms are now rarely observed (OFNWG et al., 2010). In regions where malaria is endemic or where schistosomiasis is common, typhoid may present with atypical symptoms, sometimes including polyarthritis or monoarthritis (IESRL., 2010).

Adults with typhoid fever often experience constipation, whereas infants are more prone to diarrhoea, severe toxicity, and complications such as disseminated intravascular coagulation (CCP., 2010). A particularly severe form of the disease, neonatal typhoid, can result from vertical intrauterine transmission from an infected mother, though this is rare.

Both relapses and reinfections are relatively common in typhoid fever, occurring in less than 10% of cases. Distinguishing reinfection from relapse requires molecular typing.

Diagnosis

In developing regions, the diagnosis of typhoid fever is predominantly based on clinical criteria. In areas where the disease is endemic, a fever of unknown origin lasting more than one week should be regarded as typhoid fever until proven otherwise (IDSC., 2009). It is essential to also consider differential diagnoses, including malaria, deep-seated abscesses, tuberculosis, amoebic liver abscess, and encephalitis. Additionally, awareness of the potential complications of typhoid fever is crucial, as they can often complicate both diagnosis and treatment (ECDC., 2011).

Abdominal

Gastrointestinal perforation, gastrointestinal haemorrhage, Hepatitis, Cholecystitis (usually subclinical).

Cardiovascular

Asymptomatic electrocardiographic changes, Myocarditis, Shock.

Neuropsychiatric

Encephalopathy, delirium, psychotic states, cranial or peripheral neuritis, Guillain- barre syndrome, meningitis, impairment of coordination.

Respiratory

Bronchitis Pneumonia (*Salmonella enterica* serotype typhi, *Streptococcus pneumoniae*).

Hematologic

Anaemia, Disseminated intravascular coagulation (usually subclinical), thrombocytopenia, haemolytic uremic syndrome.

Others

Focal abscess, pharyngitis, miscarriage, relapse, chronic carrier, influenza, dengue, leptospirosis, infectious mononucleosis, brucellosis, rickettsial diseases etc. should be considered (Breiman et al., 2012).

Routine blood tests

15% to 25% patients show leucopoenia and neutropenia. Leucocytosis found in intestinal perforation and secondary infection.In younger children, leucocytosis is common association and may reach 20,000-25,000/mm (Ram et al., 2007).

Liver function tests

These may be deranged. Although significant hepatic dysfunction is rare, some studies and case reports showed there was hepatic derangement simulating acute viral hepatitis and also present as hepatic abscess (Hosoglu et al., 2006).

Blood culture

The standard diagnostic method for typhoid fever is blood culture, which yields positive results in 60% to 80% of case (Srikantiah et al., 2007). Bone marrow culture is more sensitive, with a detection rate of 80% to 95%, even in patients who have been on antibiotics for several days, irrespective of the illness duration. The lower sensitivity of blood culture compared to bone marrow culture is due to the smaller number of bacteria present in the blood (Vollaard et al., 2004). Blood culture sensitivity is highest during the first week of illness and increases with the volume of blood collected ideally, 10-15 ml for school-age children and adults, and 2-4 ml for toddlers and preschool children. Notably, toddlers tend to have higher levels of bacteremia compared to adults (Dore et al., 2004).

Other cultures

Cultures can also be obtained from the buffy coat of blood, streptokinase-treated blood clots, intestinal secretions (using a duodenal string capsule), and skin snips from rose spots. The sensitivity of stool cultures is influenced by the volume of feces tested, with positivity rates increasing as the illness progresses. Stool cultures are positive in approximately 30% of patients with acute typhoid fever. The sensitivity of urine cultures varies significantly, ranging from 0% to 58% (Glynn et al., 2008).

Felix-Widal test

The classic Widal test, developed over a century ago, remains a widely used diagnostic tool for typhoid fever. It detects agglutinating antibodies against the O and H antigens of *Salmonella enterica* serotype Typhi, utilizing serum samples diluted in large test tubes (Pavia et al., 1990). Despite its simplicity, the Widal test exhibits moderate sensitivity and specificity. Reported sensitivity ranges from 70% to 80%, with specificity between 80% and 95%. It can yield false negatives in up to 30% of culture-confirmed typhoid cases due to reduced antibody response from prior antibiotic treatment (Barza et al., 2002). Furthermore, patients may exhibit no detectable antibody response or fail to show a significant rise in antibody titre.

The test's potential for false positives arises from the shared antigens of *S. enterica* serotype Typhi with other *Salmonella* serotypes and cross-reacting epitopes with other Enterobacteriaceae. To enhance diagnostic accuracy, a fourfold increase in antibody titre between acute and convalescent sera can be used if paired samples are available (Bhan et al., 2002).

Despite its limitations, the low cost of the Widal test makes it a viable option in many developing countries. Proper interpretation, taking into account the patient's history and adhering to local cut-off values for positivity, is essential for reliable results (Dunstan et al., 2001).

New diagnostic tools

The Tubex test detects IgM antibodies, while the Typhidot test identifies both IgM and IgG antibodies against the 50 kD antigen of Salmonella typhi. Preliminary studies suggest that Tubex outperforms the Widal test in terms of both sensitivity and specificity, although it has not been extensively evaluated. Despite this, culture remains the gold standard for diagnosis. The Typhidot-M test exhibits superior sensitivity (93%) compared to the culture method and offers a high negative predictive value (Dharmana et al., 2002).

In certain studies, ELISA has demonstrated superior sensitivity for total Ig estimation compared to other diagnostic methods. Recent advancements include DNA probes and polymerase chain reaction (PCR) techniques that detect *S. enterica* serotype Typhi directly from blood samples. Urine antigen detection shows a sensitivity range of 65-95%, but PCR has yet to be widely implemented in clinical practice (Crup et al., 2010).

Treatment

Prompt institution of appropriate antibiotics following early diagnosis is essential for effective management of typhoid fever. Understanding the antibiotic susceptibility of *Salmonella typhi* is crucial in selecting the most effective treatment. Over 90% of patients with uncomplicated typhoid can be managed with oral antibiotics and regular follow-up. Those with severe symptoms such as persistent vomiting, severe diarrhoea, and abdominal distension require hospitalization and parenteral antibiotic treatment (Parry et al., 2002).

Chloramphenicol was the drug of choice for typhoid fever for several decades following its introduction in 1948. Its use declined due to the emergence of plasmid-mediated resistance and serious side effects, such as bone marrow aplasia. In the 1970s, trimethoprim-sulfamethoxazole and ampicillin were used as alternatives to address chloramphenicol resistance, but these were also eventually discarded due to similar resistance issues (WHO., 2003).

By 1992, multidrug-resistant enteric fever, resistant to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, became a significant concern in Bangladesh, with approximately 36.58% of cases showing resistance (Crump et al., 1992). In response, ceftriaxone and ciprofloxacin emerged as the preferred treatments in the 1980s. Although fluoroquinolones offer excellent tissue penetration, rapid therapeutic response, and low post-treatment carriage rates, resistance to these drugs has developed in Asia over the past decade. Resistance to fluoroquinolones can be total or partial, with nalidixic acid-resistant strains showing reduced susceptibility to fluoroquinolones compared to nalidixic acid-sensitive strains (Hornick et al., 1970). While nalidixic acid-resistant isolates can still be susceptible to fluoroquinolones in disc sensitivity tests, detecting this resistance can be challenging. For nalidixic acid-resistant infections, a minimum of seven days of treatment at the highest permissible dosage is required, with 10-14 days usually necessary. According to data from the Department of Microbiology at BSMMU, nalidixic acid sensitivity is at 8.6%, while ciprofloxacin remains 67% sensitive. Although gatifloxacin was once considered superior to older fluoroquinolones, its use has been discontinued due to the need for dual point mutations for resistance and recent reports of toxicity (House et al., 2001).

Azithromycin, administered at 500 mg (10 mg/kg) once daily for seven days, has proven effective in treating typhoid fever in some adults and children, with a dose of 1 g per day for five days showing higher efficacy in adults. Among third-generation cephalosporins, oral cefixime (15-20 mg/kg per day, with adults taking 100-200 mg twice daily) has been satisfactory in various geographical settings (Everest et al., 2001), though some trials have reported higher failure and relapse rates compared to fluoroquinolones. However, sensitivity data from BSMMU show a higher efficacy of cefixime, with around 78.8% sensitivity.

Intravenous third-generation cephalosporins (ceftriaxone, cefixime, cefotaxime) are effective with low relapse (3-6%) and fecal carriage rates (<3%). Ceftriaxone, administered at 2-4 g daily in one or two divided doses, is particularly effective. Aztreonam and imipenem are potential third-line options (Bhutta., 2006).

Prevention of Typhoid Fever

In urban areas of developing countries like India and Bangladesh, rapid measures are crucial to curb the spread of typhoid fever. High infection rates are often attributed to inadequate sanitation and unsafe water. Effective prevention requires safe drinking water, proper sewage disposal, and food safety practices, such as washing hands with soap before preparing food, boiling drinking water, and avoiding raw shellfish and ice cream (Ahsan et al., 1993).

A study from Dhaka city highlighted that resident living near the Buriganga, Turag, and Balu rivers faced an elevated risk of typhoid. Factors contributing to this include the use of surface water for drinking by low-income inhabitants, as *S. typhi* can survive in water for days, making contaminated surface water a significant source of infection.

Conclusion

Typhoid fever remains a significant public health challenge, particularly in endemic regions where sanitation and access to clean water are inadequate. Despite advances in understanding the pathophysiology of the disease, challenges in diagnosis and management persist. Modern diagnostic techniques, including molecular assays and improved culture methods, have enhanced the accuracy and speed of diagnosis. Additionally, advancements in antimicrobial therapies and vaccine development offer hope for better disease control and prevention. The emergence of multidrug-resistant strains of *Salmonella Typhi* complicates treatment efforts, underscoring the need for continued research and innovation. Public health strategies focused on vaccination, improved sanitation, and education are essential for reducing the disease burden. Ultimately, a multifaceted approach that combines advances in medical science with robust public health initiatives is crucial for the effective control and eventual eradication of typhoid fever in endemic areas.

Author contributions

T., conceptualized the project, developed the methodology, conducted formal analysis, and drafted the original writing. A.R.S., contributed to the methodology, conducted investigations, provided resources and contributed to the reviewing and editing of the writing.

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Competing financial interests

The authors have no conflict of interest.

References

Acharya, I. L., Lowe, C. U., Thapa, R., Gurubacharya, V. L., Shrestha, M. B., & Cadoz, M., et al. (1987). Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of Salmonella typhi: A preliminary report. New England Journal of Medicine, 317, 1101-1104.

Ahasan, H. A., Rafiqueddin, A. K. M., Chowdhury, M. A. J., Azad, K. A. K., Karim, M. E., & Hussain, A. (1993). An unusual presentation of typhoid fever:

Barza, M., & Travers, K. (2002). Excess infections due to antimicrobial resistance: The “Attributable Fraction.” Clinical Infectious Diseases, 34(3), S126–S130.

Bhan, M. K., Bahl, R., & Sazawal, S. (2002). Association between Helicobacter pylori infection and increased risk of typhoid fever. Journal of Infectious Diseases, 186(12), 1857–1860.

Bhutta, Z. A. (2006). Current concepts in the diagnosis and treatment of typhoid fever. BMJ, 333(7558), 78–82.

Black, R. E., Levine, M. M., Ferreccio, C., Clements, M. L., Lanata, C., Rooney, J., et al. (1990). Efficacy of one or two doses of Ty21a Salmonella typhi vaccine in enteric-coated capsules in a controlled field trial. Chilean Typhoid Committee, 8, 81-84.

Breiman, R. F., Cosmas, L., Njuguna, H., Audi, A., Olack, B., Ochieng, J. B., et al. (2012). Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: Implications for typhoid vaccine use in Africa. PLOS ONE, 7(1), e29119.

Brooks, W. A., Hossain, A., Goswami, D., Nahar, K., Alam, K., & Ahmed, N., et al. (2005). Bactaeremic typhoid fever in children in an urban slum, Bangladesh. Emerging Infectious Diseases, 11, 326-329.

Centers for Disease Control and Prevention. (2010). Summary of notifiable diseases—United States, 2008. Morbidity and Mortality Weekly Report, 57(53), 94.

Chen, X., Stanton, B., Pach, A., Nyamete, A., Ochiai, R. L., & Kaljee, L., et al. (2007). Adults' perceived prevalence of enteric fever predicts laboratory-validated incidence of typhoid fever in children. Journal of Health, Population and Nutrition, 25, 469-478.

Committee on Issues and Priorities for New Vaccine Development, Division of Health Promotion and Disease Prevention, Division of International Health. (1986). New vaccine development: Establishing priorities: Diseases of importance in developing countries (p. 432). Washington, DC: National Academy Press.

Crump, J. A., & Mintz, E. D. (2010). Global trends in typhoid and paratyphoid fever. Clinical Infectious Diseases, 50(2), 241–246.

Crump, J. A., Luby, S. P., & Mintz, E. D. (2004). The global burden of typhoid fever. Bulletin of the World Health Organization, 82, 346-353.

Crump, J. A., Youssef, F. G., Luby, S. P., Wasfy, M. O., Rangel, J. M., & Taalat, M., et al. (2003). Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. Emerging Infectious Diseases, 9, 539-544.

Dharmana, E., Joosten, I., Tijssen, H. J., & Duggirala, V. (2002). HLA-DRB1*12 is associated with protection against complicated typhoid fever, independent of tumor necrosis factor alpha. European Journal of Immunogenetics, 29(3), 297–300.

Dore, K., Baxton, J., Henry, B., Pollari, F., Middleton, D., Fyfe, M., et al. (2004). Risk factors for Salmonella typhimurium DT 104 and non-DT 104 infection: A Canadian multi-provincial case-control study. Epidemiology & Infection, 132(4), 485–493.

Dunn, J., Pryor, J., Saketa, S., Wasale, D., Buadromo, E., Kishore, K., et al. (2005). Laboratory-based Salmonella surveillance in Fiji, 2004–2005. Pacific Health Dialog, 12(1), 53–59.

Dunstan, S. J., Stephens, H. A., Blackwell, J. M., Duc, C. M., Lanh, M. N., Hien, T. T., et al. (2001). Genes of the class II and class III major histocompatibility complex are associated with typhoid fever in Vietnam. Journal of Infectious Diseases, 183(2), 261–268.

Edelman, R., & Levine, M. M. (1986). Summary of an international workshop on typhoid fever. Reviews of Infectious Diseases, 8, 329-349.

European Centre for Disease Prevention and Control (ECDC). (2011). The European Surveillance System (TESSy). Stockholm, SE: ECDC.

Everest, P., Wain, J., Roberts, M., Rook, G., & Dougan, G. (2001). The molecular mechanisms of severe typhoid fever. Trends in Microbiology, 9(7), 316–320.

Gilman, R. H., Terminel, M., Levine, M. M., Hernandez-Mendoza, P., & Hornick, R. B. (1975). Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. Lancet, 1, 1211-1213.

Glynn, M. K., Reddy, V., Hutwagner, L., Shiferaw, B., Angulo, F. J., & The FoodNet Working Group. (2008). Prior antimicrobial agent use increases the risk of sporadic infections with multidrug-resistant Salmonella enterica serotype Typhimurium: A FoodNet case-control study. Clinical Infectious Diseases, 38(3), S227–S236.

Hoffman, S. L., Edman, D. C., Punjabi, N. H., Lesmana, M., Cholid, A., Sundah, S., et al. (1986). Bone marrow aspirate culture superior to streptokinase clot culture and 8 ml (1:10) blood-to-broth ratio blood culture for diagnosis of typhoid fever. American Journal of Tropical Medicine and Hygiene, 35, 836-839.

Hornick, R. B., Greisman, S. E., Woodward, T. E., DuPont, H. L., Dawkins, A. T., & Snyder, M. J. (1970). Typhoid fever: Pathogenesis and immunologic control. New England Journal of Medicine, 283(13), 686–691, and 283(14), 739–746.

Hosoglu, S., Celen, M., Geyik, M. F., Akalin, S., Ayaz, C., & Kokoglu, O. F. (2006). Risk factors for typhoid fever among adult patients in Diyarbakir, Turkey. Epidemiology & Infection, 134(3), 612–616.

House, D., Bishop, A., Parry, C., Dougan, G., & Wain, J. (2001). Typhoid fever: Pathogenesis and disease. Current Opinion in Infectious Diseases, 14(5), 573–578.

Infectious Disease Surveillance Centre. (2009). Infectious Agents Surveillance Report: Typhoid fever and paratyphoid fever in Japan. Retrieved from http://idsc.nih.go.jp/iasr/index.html

Institute for Health Metrics and Evaluation. (2012). Global burden of disease study [Internet]. Seattle, WA: Institute for Health Metrics and Evaluation. Available at: http://www.globalburden.org/. (Accessed: 3 March 2012).

Institute of Environmental Science and Research Limited, Population and Environmental Health Group. (2010). Notifiable and other diseases in New Zealand: 2009 annual surveillance report. Porirua, NZ: Institute of Environmental Science and Research Limited.

Khan, M. I., Sahito, S. M., Khan, M. J., Wassan, S. M., Shaikh, A. W., & Maheshwari, A. K., et al. (2006). Enhanced disease surveillance through private health care sector cooperation in Karachi, Pakistan: Experience from a vaccine trial. Bulletin of the World Health Organization, 84, 72-77.

Klugman, K. P., Gilbertson, I. T., Koornhof, H. J., Robbins, J. B., Schneerson, R., & Schulz, D., et al. (1987). Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. Lancet, 2, 1165-1169.

Kothari, A., Pruthi, A., & Chugh, T. D. (2008). The burden of enteric fever. Journal of Infection in Developing Countries, 2, 253-259.

Levine, M. M., Ferreccio, C., Black, R. E., & Germanier, R. (1987). Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. Lancet, 1, 1049-1052.

Levine, M. M., Ferreccio, C., Cryz, S., & Ortiz, E. (1990). Comparison of enteric-coated capsules and liquid formulation of Ty21a typhoid vaccine in randomized controlled field trial. Lancet, 336, 891-894.

Lin, F. Y., Ho, V. A., Khiem, H. B., Trach, D. D., Bay, P. V., Thanh, T. C., et al. (2001). The efficacies of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. New England Journal of Medicine, 344(17), 1263–1269.

Lin, F. Y., Vo, A. H., Phan, V. B., Nguyen, T. T., Bryla, D., Tran, C. T., et al. (2000). The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. American Journal of Tropical Medicine and Hygiene, 62(5), 644–648.

Lutui, T., Ofanoa, M., Finau, S., & Maika, K. V. (1999). Typhoid fever in Tonga. Pacific Health Dialog, 6(2), 240–244.

Lynch, M. F., Blanton, E. M., Bulens, S., Polyak, C., Vojdani, J., Stevenson, J., ... & Mintz, E. D. (2009). Typhoid fever in the United States, 1999-2006. Jama, 302(8), 859-865.

Murray, C. J. L., & Lopez, A. D. (1996). Global burden of disease and injury series (1st ed., p. 1). Boston, MA: Harvard University Press.

Ochiai, R. L., Acosta, C. J., Danovaro-Holliday, M. C., Baiqing, D., Bhattacharya, S. K., & Agtini, M. D., et al. (2008). A study of typhoid fever in five Asian countries: Disease burden and implications for controls. Bulletin of the World Health Organization, 86, 260-268.

Ochiai, R. L., Wang, X., von Seidlein, L., Yang, J., Bhutta, Z. A., & Bhattacharya, S. K., et al. (2005). Salmonella para typhi A rates, Asia. Emerging Infectious Diseases, 11, 1764-1766.

Parry, C. M., Hien, T. T., Dougan, G., White, N. J., & Farrar, J. J. (2002). Typhoid fever. New England Journal of Medicine, 347(22), 1770–1782.

Pavia, A. T., Shipman, L. D., Wells, J. G., Puhr, N. D., Smith, J. D., McKinley, T. W., et al. (1990). Epidemiologic evidence that prior antimicrobial exposure decreases resistance to infection by antimicrobial-sensitive Salmonella. Journal of Infectious Diseases, 161(2), 255–260.

Ram, P. K., Naheed, A., Brooks, W. A., Hossain, A., Mintz, E. D., & Breiman, R. F. (2007). Risk factors for typhoid fever in a slum in Dhaka, Bangladesh. Epidemiology & Infection, 135(3), 458–465.

Siddiqui, F. J., Rabbani, F., Hasan, R., Nizami, S. Q., & Bhutta, Z. A. (2006). Typhoid fever in children: Some epidemiological considerations from Karachi, Pakistan. International Journal of Infectious Diseases, 10, 215-222.

Simanjuntak, C. H., Paleologo, F. P., Punjabi, N. H., Darmowigoto, R., Soeprawoto, T., Totosudirjo, H., et al. (1991). Oral immunization against typhoid fever in Indonesia with Ty21a vaccine. The Lancet, 338(8774), 1055–1059.

Sinha, A., Sazawal, S., Kumar, R., Sood, S., Reddaiah, V. P., & Singh, B., et al. (1999). Typhoid fever in children aged less than 5 years. Lancet, 354, 734-737.

Srikantiah, P., Girgis, F. Y., Luby, S. P., Jennings, G., Wasfy, M. O., & Crump, J. A., et al. (2006). Population-based surveillance of typhoid fever in Egypt. American Journal of Tropical Medicine and Hygiene, 74, 114-119.

Srikantiah, P., Vafokulov, S., Luby, S. P., Kasymbekov, Y., Mullodzhanov, R., & Reyburn, R. (2007). Epidemiology and risk factors for endemic typhoid fever in Uzbekistan. Tropical Medicine & International Health, 12(7), 838–847.

Stuart, B. M., & Pullen, R. L. (1946). Typhoid: Clinical analysis of 360 cases. Archives of Internal Medicine (Chic), 78, 629-661.

Sur, D., Ali, M., von Seidlein, L., Manna, B., Deen, J. L., & Acosta, C. J., et al. (2007). Comparisons of predictors for typhoid and paratyphoid fever in Kolkata, India. BMC Public Health, 7, 289.

Sur, D., Ochiai, R. L., Bhattacharya, S. K., Ganguly, N. K., Ali, M., & Manna, B., et al. (2009). A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. New England Journal of Medicine, 361, 335-344.

The OzFoodNet Working Group. (2010). Monitoring the incidence and causes of diseases potentially transmitted by food in Australia: Annual report of the OzFoodNet Network, 2009. Communicable Diseases Intelligence, 34(4), 396–426.

Vollaard, A. M., Ali, S., & Van Asten, H. A. G. H. (2004). Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. JAMA, 291(21), 2607–2615.

Vollaard, A. M., Ali, S., Widjaja, S., Van Asten, H. A., Visser, L. G., Surjadi, C., et al. (2005). Identification of typhoid fever and paratyphoid fever cases at presentation in outpatient clinics in Jakarta, Indonesia. Transactions of the Royal Society of Tropical Medicine and Hygiene, 99(6), 440–450.

Wahdan, M. H., Serie, C., Cerisier, Y., Sallam, S., & Germanier, R. (1982). A controlled field trial of live Salmonella typhi strain Ty 21a oral vaccine against typhoid: Three-year results. Journal of Infectious Diseases, 145, 292-295.

World Health Organization. (2003). Background document: The diagnosis, treatment, and prevention of typhoid fever. Geneva, Switzerland: World Health Organization.

Yang, H. H., Wu, C. G., Xie, G. Z., Gu, Q. W., Wang, B. R., & Wang, L. Y., et al. (2001). Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. Bulletin of the World Health Organization, 79, 625-631.