INTRODUCTION

Estimating the typhoid fever incidence is challenging in low and middle income countries due to non-specific clinical disease presentation and limited access to blood cultures. The use of fluoroquinolones in children was not common due to reported side effects associated with joint/cartilage damage. Nevertheless, the present threat of MDR encouraged ethically supported trials of ciprofloxacin in the treatment of typhoid. The two most common disease manifestations of human Salmonella infections are gastroenteritis and typhoid fever. S. Typhi and S. Paratyphi A, can cause typhoid fever, a more severe systemic disease. Salmonellosis outbreaks linked to the consumption of fruits, leafy green vegetables, sprouts, eggs, milk products and meat. Enteric fever is systemic infection caused by Salmonella typhi and para typhi A,B and C is a significant cause of morbidity and mortality.

The two most common disease manifestations of human Salmonella infections are gastroenteritis and typhoid fever. S. Typhi and S. Paratyphi A can cause typhoid fever, a more severe systemic disease. The typhoid fever surveillance in Africa program (TSAP) revealed a significant burden of Salmonella disease in sub-African Sahara Africa.

Low moisture foods, including spices and seasonings dried protein products such as dried eggs or dried milk and seeds, have been increasingly implicated as the source of food borne Salmonellosis outbreaks.

Although most microbial hazards cannot grow in low moisture foods (LMF) due to the low water activity (aw), many pathogens can survive and remain viable for months to years in...
these foods, posing potential risks to consumers. Several national and international outbreaks of foodborne illness, as well as product recalls, have occurred in recent years due to Salmonella spp. contamination of LMF products such as spices, nuts (including peanut butter), cereal products (e.g. breakfast cereals), tahini paste, and chocolate, among many others. Recent high-profile outbreaks of foodborne illness and product recall due to microbial contamination of LMF, particularly from Salmonella spp., have increased global attention and response to the microbial safety of LMF.

Salmonella enterica sub species serovar Typhi (S. Typhi) is a major cause of invasive bacterial infection, particularly in children in low and middle-income countries. Vaccine available for prevention of typhoid fever include V1 polysaccharide vaccine (V1-PS) and live attenuated oral vaccines. Salmonella enterica, is responsible for systemic enteric fever illnesses in >20 million people worldwide each year.

Recent high-profile outbreaks of food borne illness and product recall due to microbial contamination of LMF, particularly from Salmonella spp., have increased global attention and response to the microbial safety of LMF. The fatality rate of enteric fever is low (less than 1%) but it is higher when anti microbial therapy is delayed or unavailable.

Estimating the typhoid fever incidence is challenging in low and middle income countries due to non-specific clinical disease presentation and limited access to blood cultures. Paratyphoid fever, however, often shows milder symptoms than that of S. Typhi infection.

**Chronological record of significant events**

Salmonellae are gram-negative motile bacilli. The genus Salmonella, which belongs to the family Enterobacteriaceae. Daniel E. Salmon, first isolated Salmonella. In 1880, Karl Joseph Eberth described a bacillus that he suspected was the cause of typhoid. (21) In 1884, pathologist Georg Theodor August Gaffky (1850–1918) confirmed Eberth's findings. British bacteriologist Almroth Edward Wright first developed an effective typhoid vaccine at Nutley, Hampshire.

Wright convinced the British Army, that 10 million vaccine doses should be produced for the troops being sent to the Western Front, thereby saving up to half a million lives during World War.

The British Army was the only combatant at the outbreak of the war to have its troops fully immunized against the bacterium. Theobald Smith found the bacterium in pigs. Salmonella enterica was possibly the cause of the 1576 cowpox epidemic in New Spain. Salmonella was first visualized in 1880 by Karl Eberth in the Peyer's patches and spleens of typhoid patients.

**Research program for the next generation world**

Perhaps surprisingly, Salmonella has not been identified as a principal etiological agent of diarrhea in developing countries.

**Pathogenesis**

Salmonellae produce three main types of disease in man but mixed forms are frequently observed. *Salmonella typhi* causes typhoid fever and *S. para typhi A*, B, and C cause paratyphoid fever. The food poisoning Salmonellae are prominently pathogenic for animals from whom sporadic human infections occur. *S. choleraesuis*, generally cause septicaemia. Large number of organisms are required for infection. After escaping from stomach, the organism cause infection on ilio caecal region. With the help of pilli, it attaches to M-cells. Macrophages phagocytose the bacteria. In phagosomes, the bacteria can multiply. The macrophage burst and the bacteria are released into blood. In blood, it is resistent to complements by hilling by V1-antigen.

**Clinical features**

The pathogen produces step ladder fever, Rosy spots on abdomen, Constipation in early stages, Enlargement of spleen and liver, Infection of paye’s patches and perforation of intestine. There is malaise, with increasing headache, drowsiness and aching in limbs. Cough and epistaxis are not uncommon. Constipation may present although in children diarrhea and vomiting may be prominent early. The pulse is often slower than would be expected from heights of the temperature. At the end of week typical rash may appear on the abdomen.

In addition to morbidity and mortality data, these studies will provide information on risk factors, socioeconomic impact, and the long-term implications of typhoid. The frequency and intensity of bacillary shedding vary widely and it is essential, therefore, to test repeated samples. Cholagogue purgatives increase the chance of isolation. For the detection of urinary carriers, repeated urine cultures should be carried out. The widely reaction is of no value in the detection of carriers in endemic countries. The demonstration of V1 agglutinins has been claimed to indicate the carrier state. While this is useful as a screening test, confirmation should be made by culture.

Prophylactic vaccination: Prophylactic vaccination is commonly practiced in countries with a high endemic level of typhoid fever and results of field trials have shown that vaccination confers a considerable degree of immunity against typhoid fever. Although the value of para typhoid A and B components is less certain, it is usual to give a triple TAB vaccine. The vaccine most widely employed consists of a mixture of culture of *S. typhi*, *S. paratyphi A*, and *S. paratyphi B*, killed by heating at about 60 degrees C and preserved in vaccines are less effective.

**Research on monitoring drug resistance strains of S.typhi**

Multiple drug resistance *S.typhi* is increasingly being recognized in many countries and has become a problem in India and South East Asia. In India, chloramphenicol resistant typhoid fever appeared in epidemics in Kerala in 1972 (Calicut). Subsequent reports on sporadic incidence of drug resistant strains have been made from other parts of India.
The Mechanism Involved in Typhoid Fever/Enteric Fever

In the initial stages of infection, the pathogen invades small and larger bowel walls, creating an inflammatory response. It is an intracellular pathogen. The infection spread through the body via the regional lymph nodes and bloodstream. Initial symptoms of infection are headache, fever, general malaise of infection and abdominal tenderness. Once the organism has spread throughout the body, it reaches the gall bladder and paver's patches in the colon, initiating the diarrheal stress of illness. The organism can frequently be recovered from blood and stool cultures. Appropriate antibiotic use results in clinical improvement, however, stool cultures often remain positive, which can serve as a source of infection for other individuals. Some patients can develop chronic colonization of their gall bladder, biliary tree leading to persistent shedding of the organism with potential transmission to others.

The exact mechanism responsible for diarrhea is unclear. Mucosal invasion and inflammation are clearly important, at least accounting for the bloody mucoid type of stools which occur commonly but do not explain the copious watery stool in early stages. Observations in experimental animals of enteropathy with water and electrolyte transport defects suggest the existence of secretary mechanisms.

New approaches in the discovery of Salmonella. The randomized control trials (RCT) found that people with Salmonella infection treated with norfloxacin versus placebo had significantly prolonged excretion of Salmonella species. In addition, six of nine campylobacter isolates obtained after treatment showed some degree of resistance to norfloxacin. In continued evolution of antimicrobial resistance among enteric pathogens has meant that agents previously found to be effective in clinical trials, such as trimethoprim-sulfamethoxazole or ampicillin, no longer show in vivo activity.

Molecular techniques for the detection of Salmonella

Salmonella species such as PCR, considerable advantages in terms of specificity, speed, and standardization over the conventional methodologies. However it is difficult to perform PCR directly on fecal samples due to presence of inhibitory substances and large quantities of bacterial DNA extraction from feces can be improved by pre-treating the sample with polyvinyl pyrrolidone (PVP). Commercial kits for the detection of Salmonella spp by real-time PCR. Salmonella PCR kit (Artus GmbH, Hamburg, Germany) is available but not used routinely. It is found that culture and PCR methods used for detection that Salmonella from clinical fecal samples were of similar sensitivity. However using culture results are available with 2-3 days, where those obtained by real-time PCR assays can be available within 3 hours, which can be advantageous for rapid intervention and appropriate treatment. The specimen is placed on Salmonella, Shigella (SS) agar, hektoen enteric agar, Xylose-Lysine decarboxylase (XLD) agar or deoxycholate citrate agar, which Suspect colonies are identified by biochemical reaction patterns and slide agglutination tests.

The gold standard diagnosis of enteric fever is the isolation of the organism from the blood, bone marrow, stool or urine. A number of serological assays has been over-utilized in this part of the world but need to be discouraged for the diagnosis of such acute infection. The Widal test has been in use for the past 100 years but at times, it can be misleading its potential to yield false-positive and false-negative results limit its use. Also, this assay can be misleading endemic countries and no interpretive titer should be recommended. Urinary antigen detection assays have also not been able to improve the diagnostic yield. Some rapid agglutination tests for S. typhi alone are in use, but their utility can be evaluated due to a lack of data.

The regions are amplified by polymerase chain reaction (PCR) before gel electrophoresis is done. The DNA fragments are separated on an agarose gel subjected to a pulsed electric field. Studies have reported excellent sensitivity and specificity when compared to positive and healthy controls. The turnaround time for diagnosis has been less than 24 hours.

Research on development of new diagnostic tests

Although culture remains gold standard, Typhidot-M is superior to culture method in sensitivity (93%) and has high negative predictive value. In some studies, it has shown that for total Ig estimation ELISA has superior sensitivity when compared to other tests. Recently DNA probes and polymerase-chain-reaction (PCR) have been developed to detect S. enterica serotype typhi directly in the blood.

Opening the debate on the new Typhoid Fever/Enteric Fever

Because of the efficacy and low relapse and carrier rates, associated with their use, the 4 quinolone drugs are now the drugs of choice in the treatment of adult typhoid fever has been reported. However, because of cheapness, chloramphenicol will continue to be used in other areas where the local strains are sensitive, although Azitromycin may be in the future to be a useful alternative, especially in children.

Early Recognition and Management of Enteric fever/Typhoid fever Salmonellas were the foremost of the food poisoning organisms for almost the whole of the 20th century. A dirty and unhygienic toilet is a source of many infectious diseases such as typhoid, cholera, hepatitis A and other diarrheal diseases, including parasite infestations. Hence, toilet hygiene is essential for good health. Timely and appropriate management of typhoid fever can reduce both morbidity and mortality.

Researchers struggle to develop a new treatment for Enteric fever/Typhoid fever

Chloramphenicol (500 mg 4 times daily), Ampicillin (750 mg 4 times daily) and co-trimoxazole (2 tablets or 1V equivalent twice daily) are losing their effectiveness due to resistance in many areas of the world, especially in Asia. Fluoroquinolones are the drug of choice (Eg Ciprofloxacin 500 mg twice daily) if nalidixic acid screening predicts susceptibility, but resistance is common, especially in the Indian subcontinent and also in the UK. Extended-spectrum of cephalosporins are useful alternatives but have slightly increased treatment failure rate. Azithromycin 500 mg once daily is an alternative when fluoroquinolone resistance is present.

Salmonella resistant to chloramphenicol can respond to norfloxacin, ciprofloxacin therapy. For gastroenteritis in uncompromised hosts, antibiotic therapy is often not needed and may prolong the convalescent carrier state for enteric fever appropriate antibiotics in which beta-lactams and fluoroquinolones.
Suggested Reading

11. Recalls of foods due to microbiological contamination classified by the U.S. Food and Drug Administration, fiscal years 2003 through 2011.
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