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Typhoid Fever – An Overview

Good Hygiene is the Key to Prevent Typhoid Fever

RAGHAVENDRA RAO MV*, DILIP MATHAI†, MOHAMMED KHALEEL‡, KHIZER HUSSAIN JUNAIDY#, JITHENDRA KUMAR NAIK$

ABSTRACT

All animals are susceptible to infection with *Salmonella*, a genus of Gram-negative, non-spore forming, usually motile, facultative anaerobic bacilli belonging to the family *Enterobacteriaceae. Salmonella* are differentiated into over 2,200 serologically distinct types (serotypes) based on differences in somatic, flagellar and capsular antigens. *Salmonella* Typhi causes the most severe form of enteric fever/typhoid fever. Unlike the other serotypes of *Salmonella*, humans are the only known host for this pathogen. The infection is commonly spread through fecal contaminated food and water. Typhoid fever has a slow, insidious onset and if untreated, lasts for weeks. The primary symptom is slowly rising fever often accompanied by abdominal pain. It ends either by a gradual resolution or in death due to complications (rupture of intestine or spleen). All infections occur almost always via oral route, usually with water or food contaminated by sewage or via hands of carrier.

Keywords: Vi polysaccharide vaccine, adenylate cyclase, randomized controlled trials, chloramphenicol, streptomycin, sulfonamide, tetracycline

Salmonella is a human and animal pathogen that causes considerable disease burden worldwide. The genus contains two species, *Salmonella bongori* and *Salmonella enterica.* In the United States, an estimated 11% of the foodborne illnesses are caused by *Salmonella.* The two most common disease manifestations of human *Salmonella* infections are gastroenteritis and typhoid fever. *Salmonella* Typhi and *Salmonella* Paratyphi A can cause typhoid fever, a more severe systemic disease. Salmonellosis outbreaks have been linked to the consumption of fruits, leafy green vegetables, sprouts, eggs, milk products and meat. Enteric fever is a systemic infection caused by *Salmonella* Typhi and Paratyphi A, B and C and is a significant cause of morbidity and mortality. Interactions between *Salmonella* spp. and the native microbial communities are hypothesized to contribute to the ability of this human pathogen to colonize. The typhoid fever surveillance in Africa program (TSAP) revealed a significant burden of *Salmonella* disease in sub-Saharan Africa. Low moisture foods (LMF), including spices and seasonings, dried protein products, such as dried eggs or dried milk and seeds, have been increasingly implicated as the source of foodborne Salmonellosis outbreaks.

Although most microbial hazards cannot grow in LMFs due to the low water activity (a_w), 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 illnesses, 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 recalls due to microbial contamination of LMF, particularly from *Salmonella* spp., have increased global attention and response to the microbial safety of LMF.

S. enterica subspecies serovar Typhi *(S.* Typhi) is a major cause of invasive bacterial infection, particularly in children in low- and middle-income countries. Vaccines available for prevention of typhoid fever include

*Scientist-Emeritus and Director of Central Research Laboratory
†Professor of Medicine and Dean
Apollo Institute of Medical Sciences and Research, Hyderabad, Telangana
‡Professor of Microbiology, Clinical and Diagnostic Microbiologist
Dept. of Microbiology, Deccan College of Medical Sciences, Hyderabad, Telangana
#Resident, Dept. of Pharmacology, Gandhi Medical College, Secunderabad, Telangana
$Professor of Toxicology, Dept. of Zoology, Osmania University, Hyderabad, Telangana
Address for correspondence
Dr MV Raghavendra Rao
Scientist-Emeritus and Director of Central Research Laboratory
Apollo Institute of Medical Sciences and Research, Hyderabad, Telangana
E-mail: reachdrmvrrao@gmail.com; Dr.rao_m@apolloimsr.edu.in

Vi capsular polysaccharide vaccine (Vi-CPS) and live attenuated oral vaccine Ty21a.

Vaccination against *S.* Typhi using the Vi-CPS, a T-cell independent antigen, can protect from the development of typhoid fever. This implies that antibodies to Vi alone can protect in the absence of a T-cell-mediated immune response; however, protective Vi antibodies have not been well-characterized.

Enteric fever is principally caused by *S. enterica* serovar Typhi *(S.* Typhi*). S.* Typhi is the leading pathogen isolated from blood cultures in South Asia.

The fatality rate of enteric fever is low (<1%) but it is higher when antimicrobial therapy is delayed or unavailable.

Alternative molecular serotyping methods have been described previously, including pulsed-field gel electrophoresis, sequence-based polymerase chain reaction (PCR) (rep-PCR) and combined PCR- and sequencing-based approach that directly targets O- and H-antigen-encoding genes.

Paratyphoid fever, however, often shows milder symptoms than that of *S.* Typhi infection.

Typhoid *Salmonellae* are human-restricted, and nontyphoidal *Salmonella* (NTS) are broad host-range serovars infecting both humans and animals.

Symptoms of typhoid include fever, headache, weight loss, lethargy, stupor, malaise, leukopenia, thrombocytopenia, gastrointestinal bleeding and neurological complications.

Healthy carriers shed *S.* Typhi in their stool, which passes on the bacterium through the contamination of food and water sources.

CHRONOLOGICAL RECORD OF SIGNIFICANT EVENTS

Salmonellae are Gram-negative motile bacilli. The genus *Salmonella* 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.

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 the Army Medical School in Netley, Hampshire. It was introduced in 1896 and was used successfully by the British during the Boer War in South Africa.

Karl Joseph Eberth, doctor and student of Rudolf Virchow, in 1879 discovered the bacillus in the abdominal lymph nodes and the spleen. He went on to publish his observations in 1880 and 1881. His discovery was then verified and confirmed by German and English bacteriologists, including Robert Koch.

The genus "*Salmonella*" was named after Daniel Elmer Salmon, an American veterinary pathologist, who was the administrator of the USDA research program, and thus the organism was named after him, despite the fact that several scientists had contributed to the quest.

In 1909, Frederick F Russell, a US Army physician, adopted Wright's typhoid vaccine for use with the army, and 2 years later, his vaccination program became the first in which an entire army was immunized. It eliminated typhoid as a significant cause of morbidity and mortality in the US military.

As a cook of Sloane Maternity in Manhattan, Mary Mallon contaminated, over a period of 3 months, at least 25 people, doctors, nurses and staff. Two of them died. She had managed to be hired as "Mary Brown". Since then, she was stigmatized as "Typhoid Mary" and became the butt of jokes, cartoons and eventually "Typhoid Mary" appeared in medical dictionaries, as a disease carrier.

Both salmonellosis and the microorganism genus *Salmonella* derive their names from a modern Latin coining after Daniel E Salmon.

CLINICAL PRESENTATION

Without treatment, some patients develop sustained fever, bradycardia, hepatosplenomegaly, abdominal symptoms and occasionally, pneumonia. In white-skinned patients, pink spots, which fade on pressure, appear on the skin of the trunk in up to 20% of cases. In the third week, untreated cases may develop gastrointestinal and cerebral complications, which may prove fatal in up to 10-20% of cases. The highest case fatality rates are reported in children under 4 years. Around 2-5% of those who contract typhoid fever become chronic carriers, as bacteria persist in the biliary tract after symptoms have resolved.

THE MECHANISM INVOLVED IN TYPHOID FEVER/ ENTERIC FEVER

Enteric fever is endemic in many developing countries due to poor sanitation and substandard water supply.

Enteric fever is caused due to infection by the genus *Salmonella,* which comprises of *S.* Typhi, *S.* Paratyphi A, *S.* Paratyphi B, *S.* Paratyphi C. All these organisms can cause a bacteremic illness known as 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 is spread to the body via the regional lymph nodes and bloodstream. Initial symptoms of infection are headache, fever, general malaise and abdominal tenderness. Once the organism has spread throughout the body, it reaches the gallbladder and payer's patches in the colon, initiating the diarrheal 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 gallbladder, biliary tree, leading to persistent shedding of the organism with potential transmission to others.

S. Typhi is a human host-restricted pathogen that is responsible for typhoid fever in approximately 10.9 million people annually. The typhoid toxin is postulated to have a central role in disease pathogenesis, the establishment of chronic infection and human host restriction.

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.

Production of prostaglandins and other mediators by the inflammatory tissues and toxin production by the organisms have been suggested. *Salmonella* produces an enterotoxin and a cytotoxin. The enterotoxin activates adenylate cyclase and has some physicochemical characteristics in common with cholera toxin but limited antigenic homology.

Typhoid fever is caused by the bacterium *S. enterica* subsp. *enterica* serovar Typhi. It is mainly due to the inadequate access to safe water and sanitation, which is a major problem in developing countries. The global burden of typhoid fever was estimated to be 12 million cases and 1,30,000 deaths in the year 2010. It exceeded 100 cases per 1,00,000 people/year in South East Asian countries, and has especially high burden rates in India. A recent systematic review and meta-analysis estimated the prevalence of laboratory confirmed typhoid and paratyphoid cases in India to be 9.7 and 0.9%, respectively.

NEW APPROACHES IN THE DETECTION OF *SALMONELLA*

Randomized controlled trials (RCTs) have 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.

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* species such as PCR, offer 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 polyvinylpyrrolidone (PVP).

It has been found that culture and PCR methods used for detection of *Salmonella* from clinical fecal samples were of similar sensitivity. However, culture results are available in 2-3 days, whereas those obtained by real-time PCR assays can be available within 3 hours, which can be advantageous for rapid intervention and appropriate treatment.

RECENT ADVANCES IN DIAGNOSTIC TECHNOLOGY

In enteric fever and septicemia, blood culture results are often positive in the first week of the disease.

In enteric fever, the stools yield positive results from the second or third week on. In enterocolitis, the stools yield positive results during the first week. Bone marrow cultures may be useful. Urine culture reports may be positive after the second week. A positive culture of duodenal drainage establishes the presence of *Salmonellae* in the biliary tract in carriers. EMB, MacConkey or deoxycholate medium permits rapid detection of lactose nonfermenters (not only *Salmonellae* and *Shigellae* but also *Proteus, Pseudomonas,* etc.) Bismuth sulfate medium permits rapid detection of *Salmonellae,* which form black colonies because of H2S production. Many *Salmonellae* produce H2S.

The specimen is plated on *Salmonella-Shigella* (SS) agar, hektoen enteric (HE) agar, Xylose-lysine decarboxylase (XLD) agar or deoxycholate-citrate agar, which favors the growth of *Salmonellae* and *Shigellae* over other

Enterobacteriaceae. The stool specimen is also put into selenite F or tetrathionate broth. Both of these inhibit replication of normal intestinal bacteria and permit multiplication of *Salmonellae*. After incubation for 1-2 days, this is plated on differential selective media. Suspect colonies are identified by biochemical reaction patterns and slide agglutination tests.

Hektoen enteric agar was introduced in 1968 by Sylvia King and William I Metzger. They formulated HE agar medium while working at the Hektoen Institute in Chicago, to increase the recovery of *Salmonella* and *Shigella* from clinical specimens. It is a selective as well as differential medium. HE agar is currently used as both a direct and indirect plating medium for fecal specimens to enhance the recovery of species of *Salmonella* and *Shigella* from heavy numbers of mixed normal fecal flora.

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 overutilized 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 limits its use. This assay can be misleading in 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 cannot be evaluated due to a lack of data.

BIOTECHNOLOGY OF MOLECULAR DIAGNOSIS OF ENTERIC FEVER

Detection methods rely on traditional bacterial culture procedures that employ the use of serial enrichments with increasing selectivity culminating in the isolation of *Salmonella* on selective-differential agar plates.

Even with newer automated technologies that permit simultaneous testing of multiple analytes, at least 24 hours are needed for confirmation of *Salmonella.*

DNA fingerprinting techniques, such as pulsed-field gel electrophoresis (PFGE), ribotyping and intergenic sequence (IGS) ribotyping, have all been used to subtype *Salmonella* isolates.

For ribotyping, genomic DNA is digested, separated on an agarose gel and then hybridized to rRNA operons to visualize the banding pattern.

After comparison to a database of fingerprints species, serovar and occasionally strain identifications can be made.

The DNA fragments are separated on an agarose gel subjected to a pulsed electric field. DNA is visualized by ethidium bromide staining and fingerprints are analyzed using specific software.

PCR as a diagnostic modality for typhoid fever was first evaluated in 1993 when Song et al successfully amplified the flagellin gene of *S.* Typhi in all cases of culture proven typhoid fever and from none of the healthy controls. 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.

OPENING THE DEBATE ON THE MANAGEMENT OF TYPHOID FEVER/ENTERIC FEVER

Because of the efficacy and low relapse and carrier rates, associated with their use, the four quinolone drugs are now the drugs of choice in the treatment of adult typhoid fever.

However, because of cheapness, chloramphenicol will continue to be used in areas where the local strains are sensitive. Azithromycin may be in the future a useful alternative, especially in children.

Early Recognition and Management of Enteric Fever/Typhoid Fever

Salmonellae 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 parasitic infestations.

Hence, toilet hygiene is essential for good health. Timely and appropriate management of typhoid fever can reduce both morbidity and mortality. During the past two decades, *Salmonella enteritidis* has emerged as a leading cause of human infections in many countries, with hen eggs being a principal source of the pathogen. This has been attributed to this serovar's unusual ability to colonize ovarian tissue of hens and be present within the contents of intact shell eggs. Broiler chicken is the main type of chicken consumed as poultry in many countries. Large percentages are colonized by *Salmonellae* during grow-out and the skin and meat of carcasses are frequently contaminated by the pathogen during slaughter and processing. Considering the major role eggs and poultry have as vehicles of human cases of salmonellosis, an assessment of different factors affecting

the prevalence, growth and transmission of *Salmonella* in eggs and on broiler chicken carcasses and the related risk of human illness would be useful to risk managers in identifying the intervention strategies that would have the greatest impact on reducing human infections.

RESEARCHERS STRUGGLE TO DEVELOP A NEW TREATMENT FOR ENTERIC FEVER/TYPHOID FEVER

Patients with persistent vomiting, inability to take oral food, severe diarrhea and abdominal distention usually require parenteral antibiotic therapy, preferably in a hospital. Antibiotic therapy must be guided by *in vitro* sensitivity testing.

Chloramphenicol (500 mg 4 times daily), ampicillin (750 mg 4 times daily) and co-trimoxazole (2 tablets or IV equivalent twice daily) are losing their effectiveness due to resistance in many areas of the world, especially India and South East Asia. Fluoroquinolones are the drugs of choice (e.g., 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 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 include beta-lactams and fluoroquinolones.

With the limitations of the two existing *Salmonella* vaccines, particularly their lack of effectiveness in young children, along with their lack of widespread uptake in endemic countries, the *Salmonella* community and global health policymakers are keenly awaiting the arrival of new vaccines against *Salmonella.* Vaccine is indicated for those persons who travel or live in areas where typhoid fever is endemic. Multidrug resistance transmitted genetically by plasmids among the strains of *S.* Typhi had been reported for the first time in 1972 from Mexico. The transmissible plasmids carry R determinants to chloramphenicol, streptomycin and sulfonamide and tetracycline. Multiple drug resistance has become a problem in India and South East Asia. Chloramphenicol-resistant typhoid fever had appeared first in epidemic form in Kerala (Calicut), India in 1972. The drug-resistant strains of *S.* Typhi that had been reported from India were originally confined to include phase D1-N, but later to types C5, A and O.

Prevention

Handwashing with soap and water is the simplest and also the most economical way to remove dirt and prevent the transmission of harmful microorganisms and control the spread of infection. But, it is important to choose the right type (quality) of soap. The quality (or grading) of soap is determined by the total fatty matter (TFM), defined as the total amount of fatty matter (fatty acids - oleic, stearic and palmitic), which can be separated from a sample after splitting with mineral acid (hydrochloric acid).

Hand hygiene is inexpensive and forms an integral part of infection control practices in healthcare. Our hands are home to two types of bacterial flora - the resident flora and the transient flora.

The resident flora is found in the deeper layers of skin. Proper sewage disposal, correct handling of food and good personal hygiene are important for prevention. Between 1995 and 2008, Bangladesh made significant progress in providing improved sanitation services throughout the country.

Vaccination is recommended for people who travel from developed countries to endemic areas including Asia, Africa and Latin America.

AN OPINION ARRIVED AT THROUGH A PROCESS OF REASONING

Outbreaks make the news, but most cases occur in individuals or as sporadic events.

Current surveillance systems remain insensitive to diffuse and sporadic cases and resources for laboratory investigations are limited. Food-borne illnesses are an important public health challenge. The new discoveries are probably a result of - 1) Recent acquisition of key virulence factors and 2) Detection of newly developed laboratory methodologies.

There is a need for education programs that inculcate the importance of good agriculture practices, as well as safe post-harvest handling and preparation of food.

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US$675 Million Required for New Coronavirus Global Preparedness and Response Plan

In order to fight further spread of the new coronavirus outbreak in China and across the globe, and protect states with weaker health systems, the international community has launched a US$675 million preparedness and response plan covering the months of February to April 2020.

"My biggest worry is that there are countries today who do not have the systems in place to detect people who have contracted the virus, even if it were to emerge," said Dr Tedros Adhanom Ghebreyesus, WHO Director-General. "Urgent support is needed to bolster weak health systems to detect, diagnose and care for people with the virus, to prevent further human to human transmission and protect health workers." (*WHO*)

Global Measles Vaccination Campaign to Protect up to 45 Million Children

Gavi, the Vaccine Alliance, is set to help vaccinate up to 45 million children in 7 developing countries over the next 6 months in a series of major vaccination campaigns to curb a recent rise in global measles cases.

The campaigns will be conducted by governments with funding from Gavi and support from Vaccine Alliance and Measles & Rubella Initiative (M&RI) partners, including the WHO and UNICEF. The focus will be on children under 5 years old, with Bangladesh also aiming to reach children under 9 years of age… (*UNICEF*)

Lower Glucose Treatment Threshold OK for Newborn Brain

Lower glucose targets for otherwise healthy newborns at risk for hypoglycemia did not result in worse cognition in a randomized noninferiority trial. Compared to the traditional treatment threshold of 47 mg/dL, giving treatment to newborns only when the glucose level fell below 36 mg/dL led to similar average cognitive scores at 18 months (102.9 for lower threshold vs. 102.2, mean difference 0.7, 97.5% CI -1.5 to 2.9), reported researchers in the *New England Journal of Medicine*.