

Recent advancement in Typhoid research - a review

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Abstract

Typhoid fever is endemic in South and Central America, the Middle East, South East and Far East Asia and the Indian subcontinent. It is estimated that more than 33 million cases of typhoid fever occur annually causing more than 500,000 deaths. *Salmonella* organism are extensively distributed in nature and causing widespread of disease in men and animals. *Salmonella enterica* serotype *typhi* causes typhoid fever, which is classically characterized by fever, headache, rose-colored rash, abdominal pains, diarrhea, paradoxical bradycardia and various other symptoms. This article discusses and summarizes important work in the literature in response to the epidemiology of typhoid fever, *salmonella* related to international trade and use of animal model to study typhoid. In this communication, we also reviewed the pathogenesis of *Salmonella* organism, diagnosis of typhoid fever and its treatment. Vaccination in relation to typhoid fever has been also focused. This review will let the reader to have a retrospective study on typhoid in concerned with *Salmonellae*.

Key words: Salmonellae, typhoid fever, vaccine, pathogenesis, drug resistance

et al., 2003), Spain (Ruiz *et al.*, 2003) and Nigeria (Agbakwuru *et al.*, 2003). A number of reports regarding the epidemiology of this disease have been made (Dimitrov *et al.*, 2007; Perera *et al.*, 2007; McGovern *et al.*, 2007; Paris *et al.*, 2008).

Salmonellae

Salmonellae are aerobic, non-spore-forming, flagellated bacilli. *Salmonella typhi*, the etiologic agent for typhoid fever, is a member of the *salmonella* genus which belongs to the Enterobacteriaceae family of Gram negative bacteria. Members of this genus have a variety of pathogenic effect (Table 1). *Salmonella typhi* cells are rod shaped 2-3 µm long and 0.4-0.6 µm diameter. *Salmonella* strains have evolved to infect a wide variety of reptiles, birds and mammals resulting in many different syndromes ranging from colonization and chronic carriage to acute fatal diseases. Differences in lipopolysaccharide (LPS) generate the antigenic variations, which also affect the virulence of the strain (Fierer and Guiney, 2001). The SPI-1 cell invasion function enabled the *Salmonella* to establish separate niche in epithelial cells. The *mgcA* locus on SPI-3 is also present in all cell lineages and

Introduction

Typhoid fever is an infectious disease of global distribution (House *et al.*, 2001). It is a systemic infection caused by *Salmonella enterica* serotype *typhi*, remains an important worldwide cause of morbidity and mortality (Crum, 2003). It is a prolonged febrile illness and continues to be a health problem in developing countries where there is poor sanitation, poor standard of personal hygiene and prevalence of contaminated food. It is endemic in many parts of the developing world, and as global travel increases, illness can and do occur around the world in span of a day (Lifshitz, 1996). In urban areas where sewage disposal is lacking or inadequate, water supplies get contaminated and thus cause the outbreaks of typhoid. The contamination of food by carrier is the second most frequent route of infection (Hornick, 1985). A number of reports on typhoid were made (Sharma *et al.*, 2005; Toovey, 2006; Hirschhorn and Greaves, 2007; Stejskal, 2007; Ochiai *et al.*, 2008).

Epidemiology

Typhoid fever was reported to be endemic in Far East Asia, Middle East, Central and South America. It remains a serious problem in Zimbabwe (Pithie, 1993), Australia (Skull and Tallis, 2001), Western French Guiana (Mallic *et al.*, 2001), Thailand (Swaddiwudhipong *et al.*, 2001), Ivory coast, India (Kumar *et al.*, 2001; Saha *et al.*, 2002), Florida (Katz *et al.*, 2002), Turkey (Hosoglu

Table 1: Pathological changes in typhoid fever.

S.No	Organ	Pathological Changes
1.	Heart	Heart may get enlarge and affected by fatty degeneration.
2.	Skin	Skin changes with collection of bacilli, which cause the classical rose spots.
3.	Liver	Liver get enlarged with fatty changes.
4.	Peyer patches	Peyer patches vary from hyperplasia and ulceration, through to frank ulceration and typhoid perforation.
5.	Spleen	Spleen becomes large and soft.
6.	Kidney	Kidney show cloudy swelling which may results in albuminuria.
7.	Lungs	Bronchitis is common in typhoid fever.
8.	Gall bladder	Cholecystitis may lead to the formation of infected gall stones in the gall bladder which may be a potent source of infection in the typhoid carrier.

Table 2: Changing resistance pattern of *S. enterica* serotype typhi strains isolated at Kolkata, India.

Year	Ampicilin	Chloramphenicol	Cotrimoxazole	Tetracycline	Ciprofloxacin
1990-1992	All strain 100% resistant	All strain 100% resistant	All strain 100% resistant	All strain 100% resistant	All strain 100% resistant
1993-1997	30-35% strain regained susceptibility	30-35% strain regained susceptibility	30-35% strain regained susceptibility	30-35% strain regained susceptibility	30-35% strain regained susceptibility
1990-1999					All strains isolated during 1990-1999 were uniformly (100%) resistant to ciprofloxacin
2000	40% strain susceptible to Ampicilin	50% susceptible to Chloramphenicol	40% strain susceptible	50% susceptible	Nine strains of typhi showed resistant to ciprofloxacin

facilitates the adaptation of bacteria to the low Mg²⁺, low PH environment of the endosome that result from SPI-1 mediated invasion. Subsequent acquisition of SPI-2 allowed *Salmonella* to manipulate the sorting of the endosome or phagosome, altering the intracellular environment and facilitated bacterial growth within infected cells. The ability of bacteria to disseminate from the bowel and establish extra intestinal niches is facilitated by the *spv* locus.

Multi-Drug Resistant *S. typhi* (MDRST)

The emergence of multi drug resistance to *S. typhi* (MDRST) has been of major concern in recent years. MDRST is defined as strains of *S. typhi* resistant to all three first line antibiotics for typhoid fever. The number of reported multi resistant typhoid fever increased rapidly through out the world from 1989 onwards with most of the cases from the Middle East and Asia especially in the Indian subcontinent, Pakistan and China. Resistance to these agents is associated with the plasmid present in the bacteria. Changing resistance pattern of *S. enterica* serotype typhi strains isolated at Kolkata, India were listed in the table 2.

Salmonella and the international food trade

A rapidly growing international trade in agricultural, aqua cultural and manufactured

food products has greatly facilitated the introduction of new *Salmonella* serovars within the geographical boundaries of importing countries. Various foods borne Salmonellosis have been reported (Gomez *et al.*, 1997). Moreover the prevalence of *Salmonella* organism in food viz-fresh fruits, vegetables, spices, cheese that are subject to the import export market have been studied. (D'Aoust, 1994). Typhoid fever also remained a significant public health problem among consumers of raw molluscum shellfish (Rippey, 1994). Moreover the fruit juice borne outbreaks of typhoid and other diseases in 1900s have also been reported (Parish, 1997). A number of contaminated foods that caused *Salmonella* infection are listed in the table 3.

Table 3: Prevalence of *Salmonella* in selected food types that are subjected to the import-export market.

S.No	Food Stuff
1.	Aqua culture products
2.	Cheese
3.	Fresh fruit
4.	Orange juice
5.	Raw Molluscan Shellfish
6.	Spices
7.	Vegetables

Pathogenesis

S. typhi and *S. paratyphi* A and B are highly invasive bacteria that pass through the intestinal mucosa of humans rapidly and

efficiently to eventually reach the reticuloendothelial system, where, after 8 to 14 days of incubation period, they participate in a systemic illness. Susceptible human hosts ingest the causative organisms in contaminated food or water. The inoculum size and the type of vehicle in which it is ingested greatly influence the attack rate for the typhoid fever.

The ingested typhoid bacilli pass through the pylorus and reach the small intestine, rapidly penetrate the mucosal epithelium by one of two mechanisms to arrive in the lamina propria. One mechanism of invasion involves typhoid bacilli being actively taken up by M cells, the dome like epithelial cells that cover the Peyer's patches and other organized lymphoid tissue of the gut. From here, they enter the underlying lymphoid cells. In the second, quite distinct, invasive mechanism, bacilli are internalized by enterocytes where they enter membrane bound vacuoles that pass through the cell and ultimately release the bacteria at the basal portion of the cell without destroying the enterocytes. Upon reaching the lamina propria in the host, typhoid bacilli elicit an influx of macrophages that ingest the organisms but are generally unable to kill them. Some bacilli apparently remain within macrophages of the small intestinal lymphoid tissue. Other typhoid bacilli are drained into mesenteric nodes, where further multiplication and ingestion of macrophages take place. Shortly after invasion of the intestinal mucosa, a primary bacteremia is believed to take place. Ingestion of massive inoculums followed by widespread invasion of the intestinal mucosa could result in rapid and direct invasion of the blood stream. As a result of the primary bacteremia, the pathogen rapidly attains an intracellular haven through out the organs of the reticuloendothelial system, where it resides during the incubation period (Usually 8-14 days) until the onset of clinical typhoid fever. Various reports on pathogenesis of typhoid fever have been made (House *et al.*, 2001) and molecular pathogenesis of *Salmonella enterica* serotype typhimurium were also studied (Zhang *et al.*, 2003).

Molecular studies are shedding new light on the pathogenesis of human typhoid fever (Wain *et al.*, 2002). The total genomic DNA

sequence has recently been determined for a multiple drug resistant *S. typhi*, the serotype that is the cause of typhoid fever. The genome sequence showed many distinguishing features including clusters of *S. typhi* specific genes and a large number of pseudogenes. This information together with other molecular studies has provided vital clues in several important areas of typhoid biology.

Symptoms

Typhoid fever is characterized by high fever, paradoxical bradycardia, and rose colored rash out of which the most common complaints were headache, abdominal pain and diarrhea. Patient suffering from typhoid fever may develop the symptoms like digestive hemorrhages, ileocaecal perforation, encephalitides, myocarditides, enterobacterial superinfections (Leniaud *et al.*, 1984), ileal perforation (Van Basten, 1994; Rahman *et al.*, 2001), pancreatitis (Kadappu *et al.*, 2002), acute pancreatitis (Rombola and Bertuccio, 2007), intestinal perforation (Nasir *et al.*, 2008), bowel perforation (Maurya *et al.*, 1984), infarction

abscess (Singh *et al.*, 2002), hepatic dysfunction (HJH *et al.*, 2006) and hepatic abscess (Soni *et al.*, 1994). It causes septicemia of digestive origin that can cross the placenta resulting in chorioamnionitis. Maternal fetal infection with *S. typhi* can lead to miscarriage fetal death, neonatal infection as well as diverse maternal complication (Carles *et al.*, 2002). Hydatid disease of the liver complicated by Salmonellosis (Sadhu *et al.*, 1993) and Cerebral *S. typhimurium* abscess in a patient with stroke have been reported (Arentoft *et al.*, 1993).

S. typhi infection in children younger than five years of age has also been done (Mahle and Levine, 1993). The complications of typhoid fever in children include generalized edema (Madariaga *et al.*, 1995). Inflammation (Dunlap *et al.*, 1994) and acute myocarditis in non-typhoid salmonella infection were also reported (Oziol *et al.*, 1995). Various reports on typhoid related to children were also published (Balkhy, 2003; Katz, 2003). Symptoms related to organ/organ system in concerned with typhoid fever has been summarized and listed in the table 4.

Table 4: Symptoms of Typhoid fever

S.No	Symptoms	S.No	Symptoms
1.	Rose spot	16.	Bone marrow depression
2.	Relative bradycardia	17.	Eosinophilia
3.	Stepwise fever	18.	Isolated hepatomegaly
4.	Liver abscess	19.	Cardiac conduction defect
5.	Generalized edema	20.	Epistaxis
6.	Septicemia of digestive origin	21.	Intestinal haemorrhages
7.	Suppurative lymphatic abscess	22.	Pneumonitis
8.	Typhoid glomerulonephritis	23.	Severe anemia
9.	Pancreatitis	24.	Cardiovascular insufficiency
10.	Ileal perforation	25.	Myocarditis
11.	Constipation during 1st week of fever	26.	Meningitis
12.	Diarrhea during 2nd week of fever	27.	Cholecystitis
13.	Mild splenomegaly and leucopenia/ neutropenia, complicated by encephalopathy, intestinal haemorrhage and perforation during the third week	28.	Osteitis
14.	Burning micturition	29.	Thyroiditis
15.	Neutrophilia	30.	Diffuse abdominal pain

of spleen (Mehta *et al.*, 2007), typhoid glomerulonephritis (Pancharoen *et al.*, 2001), bleeding perforation, osteomyelitis of the spine, cholecystitis and cholangitis (Crum, 2003).

S. typhi has been reported to cause submandibular suppurative lymphatic

96% of cases, even when the patients have received antibiotics. Typhoid fever had been diagnosed earlier by blood culture and widal test. Widal test remained the common test for typhoid detection. Serological diagnosis of typhoid infection has been also reported (Obgol'ts *et al.*, 1985). Serological tests to measure Vi antibody using highly purified Vi antigen are available. Although this serology, including passive hemagglutination, enzyme linked immunosorbent assay (ELISA), and radioimmunoassay, is practical for the detection of chronic *S. typhi* carriers, most of whom have quite elevated levels of Vi antibody. It is of little help in diagnosing acute typhoid fever because only a minority of patient with acute infection manifest detectable Vi antibody. These test have draw back so a dot enzyme immunoassay (EIA) has been developed which detects IgM and IgG antibodies to a specific 50 Kda outer membrane protein on *S. typhi* (Jackson *et al.*, 1995).

Over the years many attempts have been made to develop tests that detect *S. typhi* antigens or nucleic acid in blood, urine, or body fluids, thereby providing a rapid diagnostic test for typhoid fever. The immunoassay is also used for the diagnosis. The immunoassay are based on the detection of the O and Vi antigens of *S. typhi* in blood or urine using coagglutination, ELISA, or counter current immunoelectrophoresis. Polymerase chain reaction (Hatta and Smits, 2007; Levy *et al.*, 2008) and DNA probe method attempt to employ *S. typhi* genes and hybridize them with labelled specific gene probes were also used.

Traditional treatment

The incidence of typhoid fever can be subsequently reduced by providing clean water and proper hygienic conditions to the population (Dhawan and Desai, 1996). The traditional treatment for typhoid fever was obtained with Chloramphenicol, Ampicillin, Trimethoprim and Sulphamethoxazole, the so-called first line antibiotics. Effective antibiotic therapy with the advent of chloramphenicol, which was first used to treat typhoid in the 1940s, has also dramatically altered the natural course of disease and reduced the mortality rate from around 25% to as low as 1%. Antibiotics that were used for the treatment of typhoid fever were listed in the table 5.

Diagnosis of typhoid

The samples used to detect salmonella organism are blood, urine, stool and bone marrow. The gold standard of bacteriological confirmation of typhoid fever is the bone marrow culture, which is positive in 85 to

Table 5: Drugs in concerned with typhoid

S.No	Drugs	S.No	Drugs
1.	Ampicillin	6.	Cotrimoxazole
2.	Azithromycin	7.	Fleroxacin
3.	Ceftriaxone	8.	Fluoroquinolone drug
4.	Chloramphenicol	9.	Norfloxacin
5.	Ciprofloxacin	10.	Ofloxacin

Short course treatment of typhoid fever

Since 1990, multidrug resistant variety of typhoid fever had been prevalent in many parts of India, caused by *S.typhi* resistant to Chloramphenicol, Ampicillin Trimethoprim and Sulphamethoxazole (John, 1996). Studies evaluating the results of short course therapy for typhoid fever have attested to the efficacy of both fluoroquinolones and third generation cephalosporins. Fluoroquinolones are efficient antimicrobial drugs for the treatment of enteric fever. The fluoroquinolone antibacterial agent fleroxacin has a broad spectrum of invitro activity which encompasses most Gram-negative species and has been used against typhoid fever (Balfour *et al.*, 1995). Quinolones treatment of bacterial enteritis is further limited because of the failure of the compounds to eradicate *Salmonella* spp (Wistrom and Noorby, 1995). Uncomplicated typhoid fever was cured by Norfloxacin, Pefloxacin and Afloxacin with a dose of 400 mg twice daily for 7-14 days or Ciprofloxacin 500 mg for 10 days (Graninger *et al.*, 1996). It is regrettable that resistance to ciprofloxacin has now emerged in MDR *S.typhi* and is a paramount importance to limit the unnecessary use of this vital drug so that its efficacy should not be further jeopardized. The treatment with Azithromycin has also been reported against typhoid (Duran and Amsden, 2000). It was then reported in the year 2006 that Ciprofloxacin therapy for typhoid fever needs reconsideration (Chitnis *et al.*, 2006). Later it was reported about Ciprofloxacin treatment failure in a case of typhoid fever caused by *Salmonella enterica* serotype Paratyphi A with reduced susceptibility to ciprofloxacin (Dimitrov *et al.*, 2007).

Vaccination

The Centre For Disease Control and

Prevention has identified immunization as the most important public health advance of the 20th century. Vaccination is an easy and highly effective way to keep travelers healthy (Sturchler and Steffen, 2001). Despite effective treatment of typhoid fever, the increasing report of MDRST make it necessary for vaccine to be used as a public health tool in developing countries. The design of new *Salmonella* vaccines, must be based on the identification of suitable virulence genes and on the knowledge of the immunological mechanisms of resistance to the disease. Control and clearance of a vaccine strain rely on the phagocyte oxidative burst, reactive nitrogen intermediates, inflammatory cytokines, CD4 (+) TCR-alpha beta T cells and are controlled by genes including NRAMPI and MHC class II. Vaccine-induced resistance to re-infection requires the presence of TH1-type immunological memory and anti-*Salmonella* antibodies. The interaction between T and B cells is essential for the development of resistance following vaccination (Mastroeni and Menager, 2003).

Considerable progress has been made in the last decade to develop vaccines against the enteric infections which is of greatest public health importance. Two vaccines against typhoid fever (Parenteral Vi polysaccharide and oral Ty21a) have been licensed in many countries (Levine and Noriega, 1993). A new typhoid vaccine composed of the Vi capsular polysaccharide has been reported (Plotkin and Bouveret 1995). Vi polysaccharide is a well standardized antigen that is effective in a single parenteral dose. It is safer than whole cell vaccine and may be used in children of two years of age or older. The Vi vaccine compares favorably with other typhoid vaccine in regard to safety, patient compliance, immunogenicity and efficacy.

Typhoid Vi capsular polysaccharide vaccine represents important additions to

immunization agents. It is immunogenic, clinically effective, and generally safe, with infrequent and usually mild adverse reaction. In the recent years there has been significant progress in the development of attenuated *Salmonella enterica* Serover typhi strains as candidate typhoid fever vaccines. In clinical trials these vaccine have been shown to be well tolerated and immunogenic. For example, the attenuated *S.enterica* var. typhi strains CVD 908-htr A (aroC aroD htrA), Ty 800 (pho P pho Q) and chi 4073 (cya crp cdt) are all promising candidate typhoid vaccine (Garmory *et al.*, 2002).

Live vaccine Ty21a given by the oral route has been exclusively tested in several studies in developing countries. Its liquid formulation was the most effective, providing more than 60% of protection after 7 years of follow up. The Vi polysaccharide vaccine has been put to trial and provided more than 65% protection; after 3 years of follow up the Vi antibody was still at a high level. These two vaccines are therefore candidates for use in public health control programs. Aromatic dependent *Salmonella* live vaccine has been also reported (Stocker, 2000). Killed whole cell bacterial vaccines of typhoid generally show a high degree of stability of potency. Live attenuated vaccines such as Ty21a typhoid vaccines loose potency through loss of viability when exposed to adverse conditions. Ty21a vaccine is susceptible to ultraviolet irradiation and has low thermal stability (Corbal, 1996). Specific antibody secreting cells (ASC) appear in the blood as a response to oral vaccination in humans. Based on information from animal experiments, these cells are believed to be migrating to the mucosa lining. A series of studies aimed at a detailed characterization of the ASC response to a prototype oral vaccine *Salmonella typhi* Ty21a with respect to its kinetic, Ig class distribution, antigen specificity, influence of the administrative route, nature of the antigen, and the corresponding antibody responses in serum.

Live *Salmonella* vaccine has been reported as a route towards oral immunization (Everest *et al.*, 1995). Live vaccines are composed of viral or bacterial strains, which are deprived of their pathogenicity but can still replicate in the organism. The preparation of vaccine

strain using gene deletion or attenuation directed mutagenesis makes it possible to develop highly genetically stable vaccines, in particular against orally transmitted bacterial diseases like typhoid fever (Saliou, 1995).

Attenuated *Salmonella* type vaccine Strain CVD 908, which harbors deletion mutation, in *aro-C* and *aro-D* has been shown to be well tolerated and highly immunogenic, eliciting impressive serum antibody, mucosal IgA and cell mediated immune response. A further derivative prepared by introducing a deletion in *htr-A* resulted in CVD 908-htr A. Both CVD 908 and CVD 908-htrA are useful as live vector vaccines to deliver foreign antigens to the immune system (Levine *et al.*, 1996).

Genetically defined live attenuated *Salmonella* vaccines are useful both as oral vaccine against Salmonellosis and for the development of multivalent vaccines based on the expression of heterologous antigens in such strains. Several candidate attenuated *S. typhi* strains are at present being evaluated as new single dose oral typhoid vaccines in human volunteers. The emergence of such a vaccine will facilitate the development of multivalent vaccines for humans.

Studies on the pathogenesis of *Salmonella* at the molecular level have lead to the identification of several classes of genes that are involved for the survival of organism in the host. This has lead to the availability of a panel of attenuated strains, which are being evaluated as oral vaccine against human and animal Salmonellosis (Chatfield *et al.*, 1994). Reports are also there for recombinant *Salmonella* vectors in vaccine development (Curtiss *et al.*, 1994). New vaccines have been licensed for typhoid and other diseases and their recommended use in adults have been reported (Gardner *et al.*, 1996; Grabenstein, 1997). Vaccination with provocative character (for example against cholera, typhoid fever, paratyphus A and B by parenteral route) should be avoided because of the danger of abortion (Stickl, 1985).

The world history and current status of typhoid fever vaccination was also reported (Gremiakova *et al.*, 1997). Attenuated *Salmonella enterica* serover *typhi* (*S.typhi*) strains can serve as safe and effective oral vaccine to prevent typhoid fever and as live vectors to deliver foreign antigens to the

Table 6: Vaccine against typhoid its composition, dose, efficacy and side effect.

S.No	Vaccine type	Composition	Dose	Efficacy	Side effects
1.	Inactivated Parenteral whole cell vaccine	It is composed of heat phenol inactivated whole cell vaccine	It is composed of heat phenol inactivated whole cell vaccine	60-67%	Frequent side effects. Severe local reactions
2.	Parenteral Capsular poly accharide vaccine Vi [ViCPs]	It is composed of virulence antigen which is the capsular polysaccharide elaborated by <i>S. Typhi</i> isolated from blood cultures.	Single injection 25 mcg (0.5 ml) No booster effect	64-72%	Well tolerated. Local mild reaction. Safe
3.	Attenuated Live Vaccine Oral Ty21a vaccine	It is live attenuated Ty21a strain of <i>S. Typhi</i>	Primary: 3-4 capsules taken on alternative day.Booster: Every five years	60-96%	Well tolerated. Fewer side effects.

immune system, either by the bacteria expressing antigens through prokaryotic expression plasmids or by delivering foreign genes carried on eukaryotic expression system (DNA vaccination). The practical utility of such live vector vaccines relies on achieving a proper balance between minimizing the vaccines reactogenicity and maximizing its immunogenicity (Pasetti *et al.*, 2003). Bacterial live vaccines *S. typhi* Ty21a has been reported to be employed as vaccine against typhoid (Dietrich *et al.*, 2003). Various reviews and reports have been done on vaccine/vaccination in concerned with typhoid fever (Levine *et al.*, 1983; Levine *et al.*, 1989; Haditsch, 2005; Guzman *et al.*, 2006; Birkenfeld, 2006; DeRoeck *et al.*, 2008; Zhang *et al.*, 2008). A number of vaccine against typhoid has been represented in the table 6.

Use of animals models to study typhoid

Various animal models to study *Salmonella* have been reported (Santos *et al.*, 2001). *Salmonella* serotype are associated with three distinct human disease syndrome viz, bacteremia, typhoid fever and enterocolitis. Most studies in *Salmonella* pathogenesis elucidate virulence mechanisms using a typhoid fever model, namely *Salmonella serotype typhimurium* infection in mice. This organism causes a typhoid fever like disease in mice, with intestinal and extra intestinal lesions closely resembling those observed in typhoid fever victims. So a murine model can be used to study typhoid.

Conclusion

Today typhoid fever is a treatable disease. It is epidemiologically feasible that it can be some day eradicated from the world. Improvement in personal hygiene, sanitation, early diagnosis, systemic screening to detect chronic typhoid careers, treatment of the careers, better treatment options using more potent drugs have all improved the outcome of typhoid fever. However, the increasing reports of MDRST is a cause for concern. Possible contributing factors, which include the misuse of antimicrobiols and migration of human populations, need to be checked. In order to reduce the incidence of human food borne salmonellosis, measure should be taken simultaneously during the production, processing, distribution, retail marketing and multiplication. Disease surveillance need to be improved. With the advent of biotechnology and various tools and techniques available, researchers have been able to fight typhoid to some extent. It is beyond doubt that in the coming times alternate system of medicine will find better therapy.

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