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"Clinical and Epidemiological Perspectives on Salmonella Typhimurium: A Comprehensive Review of Pathogenesis, Antibiotic Resistance, and Public Health Implications"

Km. Bushra Anjum*[1,3], Shikha Mishra[2,3], Prince Maurya[1,3], Kishan Singh[1,3], Rohit Yadav[2,3]
[1]Department of Pharmacology
[2]Department of Pharmaceutics
[3]Seth Vishambhar Nath Institute of Pharmacy, Barabanki-225003, U.P, India

ABSTRACT

Salmonella Typhimurium is a prominent pathogen causing numerous foodborne illnesses worldwide. This gram-negative bacterium is a subspecies of Salmonella enterica. Unlike typhoid fever, which is caused by Salmonella enterica serotype Typhi, S. Typhimurium is often transmitted through contaminated food and water. The resulting infection, called salmonellosis, manifests with gastrointestinal symptoms such as diarrhea, fever, abdominal cramps, and vomiting, typically within 6 to 72 hours after consumption. In severe cases, the infection can lead to invasive diseases like bacteremia and meningitis, posing significant risks to immunocompromised individuals, infants, and the elderly. The virulence of S. Typhimurium is primarily due to its various virulence factors, including adhesins, invasins, and toxins. These elements facilitate the bacterium's ability to attach to and invade epithelial cells, survive within host cells, and evade immune defenses. To confirm typhoid fever, isolating S. Typhi from bone marrow or blood cultures is the most reliable method. For diagnostic purposes, combining the Widal test with culturing S. Typhi from stool samples is commonly practiced. Recent advancements in genomic and proteomic technologies have enabled the identification of potential targets for new therapeutic and preventive measures, such as vaccines and antimicrobial agents. Controlling S. Typhimurium infections involves enhancing food safety practices, strengthening surveillance systems, and raising public awareness about correct food handling and preparation methods. Ongoing research is crucial to develop effective interventions and lessen the global impact of salmonellosis caused by Salmonella Typhimurium.

Keywords
•Salmonella Typhimurium
• Pathogenesis
• Virulence factors
• Host-pathogen interactions
• Antibiotic resistance
• Epidemiology

Introduction

Salmonella is a genus of rod-shaped, Gram-negative bacteria that are significant pathogens in both humans and animals. These bacteria are facultative anaerobes, meaning they can survive with or without oxygen, which contributes to their versatility and resilience in various environments. First isolated by Theobald Smith in 1855 from pigs infected with classical swine fever, the bacterium was named after his colleague, Dr. Daniel Elmer Salmon, an American pathologist (Smith, 1855). This discovery marked the beginning of extensive research into a pathogen that continues to pose significant public health challenges **[1].**

Salmonella species can be divided into two primary serotype groups: typhoidal and non-typhoidal, based on their propensity to cause particular human disorders **[2].** Non-typhoidal serotypes (NTS) are zoonotic, meaning they can spread from humans to other humans as well as between animals. While typhoidal serotypes can only be passed from person to person, they can cause bacterial infections of the intestinal tract and occasionally the bloodstream (known as typhoid fever). They can also spread throughout the body, invading organs and secreting endotoxins (the septic form). Typically, they only invade the gastrointestinal tract and cause salmonellosis **[3,4].**

Contaminated food and water can transmit S. Typhi. Once ingested, the bacteria travel from the colon through the bloodstream to the spleen, liver, and intestinal lymph nodes, where they proliferate. This condition is linked to significant morbidity and mortality, potentially impacting over 90 million individuals worldwide annually. The most prevalent manifestation of Salmonella infection globally is gastroenteritis, which is characterized by inflammation of the stomach and intestines, leading to symptoms such as diarrhea, abdominal cramps, fever, and vomiting. While typically self-limiting in healthy individuals, gastroenteritis can be severe in young children, the elderly, and immunocompromised individuals. More severe manifestations include bacteraemia, where the bacteria enter the bloodstream, and enteric fever (typhoid fever), characterized by high fever, weakness, abdominal pain, and a rash **[5]**.

Characteristics of Salmonella

Salmonella species range in size from 2-3 X 0.4-0.6 µm **[6,7,8].** Nearly all Salmonella serovars are aerogenic, with the exception of Typhimurium, which does not generate gas **[9].** Salmonella's cell wall is made up of proteins, lipoproteins, lipids, and lipopolysaccharide. The endotoxin, which is in charge of the bacterial impacts on biology, is present in the lipopolysaccharide and the lipid component of the cell wall. The somatic O antigen is another term for the endotoxin's common center polysaccharides and monosaccharides **[10].** The polysaccharide part of the bacteria's surface, which is made up of many short oligosaccharides, is known as the somatic "O" antigen. There are roughly 60 somatic antigens in Salmonella **[11].**

Classification

The classification of the genus Salmonella based on the Kauffmann-White scheme is well-established **[12,13].** According to this scheme, Salmonella consists of two species: S. enterica and S. bongori.

Within the species S. enterica, six subspecies are recognized: S. enterica subsp. enterica (I), S. enterica subsp. Salamae (II), S. enterica subsp. arizonae (IIIa), S. enterica subsp. diarizonae (IIIb), S. enterica subsp. houtenae (IV), and S. enterica subsp. indica (VI) (Popoff & Le Minor, 2001). Initially, S. bongori (V) was considered to be another subspecies of S. enterica, but it has since been classified separately as a distinct species. Salmonella bongori, as well as subspecies II, IIIa, IIIb, IV, and VI, are rarely isolated from clinical specimens but are predominantly found in cold-blooded vertebrates and environmental samples. In contrast, almost all Salmonella organisms that cause disease in humans and domestic animals belong to S. enterica subsp. enterica (I) **[14].**

Salmonella serotypes fall into two primary categories: Typhoidal and nontyphoidal

Typhoidal and nontyphoidal Salmonella

It is important to distinguish between typhoidal and non-typhoidal Salmonella because they cause various clinical manifestation although belonging to the same species. In contrast to typhoidal strains that are host-specific to humans, Salmonella typhimurium and S. enteritidis exhibit broad host specificity. When it comes to epidemiology, typhoidal Salmonella is primarily endemic in poor nations like South-East Asia and Africa, whereas NTS is prevalent worldwide. A low standard of life and an unhygienic environment could be the cause of this. Furthermore, whereas killed whole-cell parenteral vaccine, live-attenuated oral vaccination, and Vi polysaccharide capsule-based vaccine are available, there are no human vaccines for NTS **[15].**

History

In 1880, Eberth made the initial discovery of Salmonella in a patient who passed away from typhoid disease. The patient's mesenteric and splenic lymph nodes were where the organism was found. The organism was referred to as Typoid bacillus at that time **[16].** After being identified from the gut of pigs in 1884 by American bacteriologist D. E. Salmon, the organism was subsequently given the name Bacillus choleraesuis **[17,18]**. Afterwards, in 1900, Lignieres renamed the organism Salmonella Choraesuis in honor of D. E. Salmon **[19].** Based on the discovery of the O and H antigens, Kauffmann presented the one serotype, one specie theory for the genus Salmonella in 1966 **[20,21,22]**.

Transmission of Salmonella

In dry environments, salmonella is common and incredibly tenacious. It can survive in water for days or even months at a time. S. enterica serovars can infect humans and animals and have a variety of hosts and reservoirs. Both vertical and horizontal transmission are significant additional ways of transmission. Vertical transmission is crucial, particularly when it comes to Salmonella infections linked to poultry. caused by the serovar Enteritidis, which has a particular fondness for the chicken reproductive system. In this instance, systemic infection in the parent birds causes infection of the ovary and developing eggs in the oviducts, which results in transovarian infection and transmission to progeny. Conversely, horizontal transmission happens via either the aerogenous or feco-oral pathways **[23].**

Fruits and vegetables as vectors of transmission of Salmonella

The organism's adhesion to fruits and vegetables is a necessary condition for Salmonella colonization and subsequent animal and human transmission. Some S. enterica serovars, such as S. Arizona, S. Agona, and S. Heidelberg, attach to fruits and vegetables poorly, others, such S. Enteritidis, S. Typhimurium, and S. Senftenberg, cling to them effectively. Additionally, it has been revealed that S. Senftenberg's flagella are a key factor in the bacteria's adherence to fruits and vegetables. This has been seen to be the case for S. Typhimurium, albeit it can only infiltrate the mesophyll of leaves when there is light and not when it is dark. This leads to bacterial aggression at the stomata and invasion of the inner portion of the leaf's tissue. After germination, it was discovered that S.

Montenegro contaminated bean sprout seeds were still inside the developing plant, indicating that Salmonella strains can infect plant tissues, stick to their surfaces, and then spread to people and other animals **[24].**

Insects as vectors of transmission of Salmonella

In agricultural settings, insects can affect the survival and spread of bacterial diseases. In order to take use of insects as carriers, bacteria have evolved to form specific symbiotic or harmful relationships with them **[25].** Phytophagous insects are largely recognized as vectors of enteric phytobacterial pathogens that cause important diseases on many crops **[26,27].** Insects have biological and ecological characteristics (i.e., ectothermy, rapid life cycle) very different from those of animals traditionally farmed for human consumption **[28].** For examples Cockroaches and Flies which has been identified as a potential biological vector of Salmonella Enteritidis. In an experimental infection, it has been discovered that Alphitobius diaperinus, commonly referred to as the litter beetle, can spread Salmonella to chickens. In layer flocks, rodents like mice can act as Salmonella carriers, according to Bastiaan and Aize. A substantial source of S. Enteritidis genotypes and phenotypes can be found in feral mice kept in poultry farms. S. Kentucky and S. Enteritidis were the two main serovars identified from lizards and rats living in chicken barns in African nations. There is a theory that rodent and lizard excrement could contaminate the feed and litter, endangering biosecurity **[29].**

Typhoid Fever

Typhoid fever is a severe systemic illness caused by the bacterium Salmonella enterica serotype Typhi. It remains a significant public health concern, particularly in regions with inadequate sanitation and limited access to clean water. The disease is transmitted through the ingestion of food or water contaminated with the feces of an infected person **[30].**

Once ingested, the bacteria penetrate the intestinal wall and are engulfed by macrophages, allowing them to spread throughout the body via the bloodstream. The incubation period for typhoid fever typically ranges from 6 to 30 days, depending on the infective dose and the individual's health status. The clinical presentation includes sustained high fever, weakness, abdominal pain, constipation or diarrhea, and a characteristic rash known as "rose spots" **[31].**

The diagnosis of typhoid fever is confirmed through blood cultures, which isolate S. Typhi during the first week of illness. Bone marrow cultures are more sensitive and may yield positive results even after antibiotic treatment has commenced **[32].**

Treatment for typhoid fever involves the use of antibiotics, with fluoroquinolones, ceftriaxone, and azithromycin being commonly prescribed **[31].** However, the emergence of antibiotic-resistant strains of S. Typhi poses a growing challenge to treatment efforts. Preventive measures include improving sanitation, ensuring access to clean water, and vaccination with typhoid vaccines, which are recommended for people traveling to endemic areas **[33].**

Despite advances in medical treatment, typhoid fever continues to cause significant morbidity and mortality in many parts of the world. Ongoing efforts to enhance public health infrastructure, coupled with research into more effective vaccines, are crucial to combating this disease.

Virulence Factors

Type III Secretion System (T3SS)

Salmonella spp. possess a molecular mechanism known as the Type III Secretion System (T3SS). This system enables these microorganisms to inject effector proteins into the cytosol of host cells, allowing them to manipulate host cell signaling pathways to their advantage. Once inside the cell, these effectors can modify various cellular functions including cytoskeleton structure, membrane transport, signal transduction, and cytokine expression. The Type III Secretion System (T3SS) comprises numerous components, including over twenty proteins. Salmonella enterica abstracts two distinct T3SSs, termed T3SS-1 and T3SS-2, which are encoded by SPI-1 and SPI-2, respectively. T3SS-1 becomes active upon contact of the bacterium with the host cell membrane, facilitating the translocation of effector proteins into the host cell cytoplasm. On the other hand, T3SS-2 becomes active within the phagosome, facilitating the translocation of effectors into the vacuolar space **[34].**

Fimbriae

Fimbrins, a type of repeating protein that is structured helically, is the primary component of fimbriae, also known as pili, which are filamentous surface structures that are 2–8 nm broad and 0.5–10 lm long. A 7–9 kb big operon typically contains the 8–11 genes that encode proteins involved in biosynthesis, structure, and assembly. Three pathways—the nucleator-dependent pathway, the assembly pathway for type IV fimbriae, and the chaperone-usher-dependent system—have been identified for the construction of fimbriae in members of the Enterobacteriaceae family **[35].**

Flagella and flagellin

Salmonella's invasiveness may increase due to its flagellar-based motility, albeit this is still up for debate, particularly given that flagellin monomers are strong inducers of innate immunity. When macrophages become infected with Salmonella, T3SS1 translocates flagellin into the cytosol, when the inflammasome is activated and caspase-1-mediated cell death (pyroptosis) occurs. Normally, flagella are downregulated within the host; however, it has been proposed that T3SS1 might generate flagella inside macrophages, which can then be exploited for escape **[36].**

Vi antigen

The Vi capsular polysaccharide (Vi) is a crucial virulence factor of S. Typhi, encoded by the B locus, which is essential for the biosynthesis of the capsular component of the antigen. When present, the Vi capsule makes S. Typhi more invasive and lethal in attacking host cells in serum compared to other Salmonella serovars **[37].** It is possible that the Vi capsule prevents antibodies from attacking the O-antigen, which is why it prevents phagocytosis and grants serum resistance **[38,39].** The genes that encode the Vi capsule are located inside Salmonella pathogenicity island (SPI)-7's viaB locus, which is also responsible for encoding a type IVB pilus and the type III secretion system (T3SS) effector SopE **[40].**

Pathogenesis of Salmonella Infection

Salmonella infections result from the ingestion of food or water contaminated with pathogenic strains of the bacterium Salmonella enterica. Upon ingestion, Salmonella bacteria traverse the acidic environment of the stomach and reach the small intestine, where they adhere to and invade the epithelial cells lining the intestinal mucosa **[41].**

Salmonella employs an array of virulence factors to facilitate its pathogenesis. These include adhesins that mediate attachment to host cells, such as fimbriae and invasins, and secretion systems that deliver effector proteins directly into host cells, promoting invasion and survival **[42].**

Once inside the host cells, Salmonella can replicate intracellularly within specialized vacuoles called Salmonella-containing vacuoles (SCVs). This intracellular replication allows the bacterium to evade the host immune response and establish a persistent infection **[43].**

In addition to its intracellular lifestyle, Salmonella can also induce inflammation in the intestinal mucosa, leading to the characteristic symptoms of gastroenteritis, including diarrhea, abdominal pain, and fever. This inflammatory response is triggered by the activation of host innate immune pathways, such as the NF-κB pathway, in response to Salmonella lipopolysaccharide (LPS) and other pathogen-associated molecular patterns (PAMPs) **[44].**

In some cases, Salmonella can breach the intestinal barrier and disseminate systemically, leading to more severe manifestations of disease, such as bacteremia and typhoid fever. Systemic dissemination may occur via translocation across the intestinal epithelium or through invasion of M cells in the Peyer's patches of the small intestine **[45].**

The host immune response plays a critical role in controlling Salmonella infection. Innate immune cells, such as macrophages and dendritic cells, recognize and phagocytose Salmonella, initiating an inflammatory response and activating adaptive immunity **[46].** T lymphocytes, particularly CD4+ T cells, are essential for clearing intracellular Salmonella and preventing systemic spread **[47].**

Salmonellosis can be divided into three major categories: gastroenteritis, invasive non-typhoidal salmonellosis and enteric (typhoid or paratyphoid) fever. Enteric fever is caused by the typhoidal salmonella serovars Typhi and Paratyphi while gastroenteritis and invasive non-typhoidal salmonellosis are caused by nontyphoidal serovars, most commonly S.typhimurium and Salmonella Enteriditis.

Gastroenteritis

Salmonella gastroenteritis typically manifests between 8 to 72 hours post-infection (p.i.) and is usually self-limiting, resolving within 3 to 7 days. The pathology is localized to enterocolitis, an inflammation of the gastrointestinal tract, with symptoms such as abdominal pain, vomiting, diarrhea, and fever. However, some patients may experience more severe hemorrhagic enterocolitis, characterized by bloody and purulent stool **[48,49].** The disease is transmitted via the fecal-oral route through the ingestion of contaminated food and water. Initially, Salmonella colonizes the ileum, followed by the Peyer's patches and mesenteric lymph nodes (MLNs). This polymorphonucleocytes (PMNs) recruitment results in a high level of exudate in the intestinal lumen, causing diarrhea. Consequently, the most significant health risk is dehydration, which can be managed with fluid and electrolyte therapy **[48].**

Invasive nontyphoidal Salmonellosis

In regions where the epidemiology of Salmonella serovars causing gastroenteritis in otherwise healthy individuals (mainly S. Enteritidis and S. Typhimurium) overlaps with immunosuppressive factors such as child malnutrition and adult infections with HIV and malaria, the disease can become invasive and systemic, posing a much greater threat to life **[50,51,52,53].** This is particularly prevalent in Africa, where the incidence of invasive nontyphoidal salmonellosis (iNTS) is about 3 cases per 1000 individuals per year **[54].** If left untreated, the mortality rate is 20-

25%, but it can rise to 50% if the infection reaches the meninges. Clinical manifestations of the disease vary among patients, with commonly observed symptoms often resembling those of enteric fever **[55].** If an individual's immune system is compromised when infected with nontyphoidal Salmonella, the bacteria can breach the gastrointestinal tract and enter the bloodstream **[50].** Suppressed adaptive immunity can hinder complement-mediated killing, significantly enhancing Salmonella's survival in the blood **[56].** This is particularly important because complement is crucial for an optimal oxidative burst during the phagocytosis of nontyphoidal Salmonella by immune cells **[57].** The primary treatment for invasive nontyphoidal Salmonella (iNTS) is antibiotic therapy; hence, factors contributing to antibiotic resistance and tolerance in the pathogen are of significant concern.

Enteric fever

Known by many names as typhoid fever, enteric fever is a prevalent infectious disease in low- and middle-income nations **[58].** It is the most frequent bacterial cause of fever among migrants and travelers who are returning from these regions **[59,60].** According to estimates from the Global Burden of Disease Study in 2017, some 14 million people are affected each year, with 136,000 fatalities, mostly in low and middle income countries. Typhoid fever and paratyphoid fever are both classified as enteric fevers and are brought on by infections with the Salmonella Typhi (S Typhi) bacteria. Worldwide estimates place the cause of 76% of enteric fever at S. Typhi. The majority of cases of paratyphoid fever occur in China and South Asia **[58,61].** Infection results from consuming food or water tainted by human feces **[62].**

Up to 161,000 deaths and 21 million cases of enteric fever are reported globally each year, according to WHO **[63].** But according to a recent study on the prevalence of typhoid and paratyphoid fever worldwide in 2017, enteric fever deaths decreased by 41% from 1990 to 2017 **[64].** Enteric fever can present with a wide range of symptoms that can mimic those of other systemic disorders. It comprises hepatomegaly, splenomegaly, leukopenia, thrombocytopenia, vomiting, diarrhea, constipation, anorexia, stomach pain, and relative bradycardia. A clinical diagnosis of enteric fever can be challenging because the symptoms and sequelae might also differ based on an individual's age. Anemia, gastrointestinal hemorrhage, intestinal perforation, hypoplasia of the bone marrow, encephalopathy, disseminated intravascular coagulation, and shock are frequent side effects **[65,66].**

Epidemiology for enteric fever

The incidence of enteric fever was estimated to be 22 million cases worldwide in 2000, with 200,000 deaths, mostly in developing nations. Regional variations exist in the incidence and fatality rates of enteric fever; nonetheless, even with antibiotic therapy, the mortality rate can reach 7% **[67].** Many parts of the African and Asian continents, as well as nations in the Middle East, South and Central America, and Europe, have endemic cases of enteric fever. In the United States and several European countries, the frequency of enteric fever is rather low, with fewer than 10 cases of Salmonella per 100,000 people annually. Travel is a factor in the majority of cases reported in these nations; foreigners or travelers returning from Pakistan, India, or Africa are the ones that bring the disease with them **[68,69].** Enteric fever is extremely rare in Israel; between 1995 and 2003, the number of cases per 100,000 people decreased from 0.42 to 0.23. Nonetheless, the causal organism pattern indicates a

growing incidence of S. Paratyphi cases; in Israel, this organism was identified from 57.4% of patients who had enteric fever **[70].** This seems to be consistent with the global rise in S. pneumoniae infections, particularly in Asian nations where these strains account for over half of the frequency of gastroenteritis **[71].** With more than 100 cases per 100,000 people yearly, some Asian nations—including China, India, Vietnam, Pakistan, and Indonesia—have high incidence rates of enteric fever. With 451.7 cases and 214.2 cases per 100,000 people, respectively, Pakistan and India have the highest incidence rates among other Asian nations **[72].** Enteric fever is more common in newborns, preschoolers, and school-age children in endemic areas. According to recent epidemiological studies, the yearly incidence of enteric fever in children under the age of five was roughly 25 per 100,000 people in China and Vietnam, whereas it could reach as high as 450 per 100,000 people in India and Pakistan **[73].**

Epidemiology for Non-typhoidal *Salmonella* infections

Non-typhoidal Salmonella (NTS) infections are the most common form of Salmonella infections worldwide, typically causing self-limited illness. These infections are prevalent across diverse geographical regions and affect individuals of all ages and backgrounds. The transmission of NTS occurs primarily through the consumption of contaminated food, particularly poultry, eggs, meat, and dairy products, as well as through contact with infected animals or their environments. While NTS infections often result in gastroenteritis characterized by symptoms such as diarrhea, abdominal pain, and fever, severe cases may lead to complications such as bacteremia, particularly in immunocompromised individuals or those with underlying health conditions. The incidence of NTS infections varies widely across different populations and settings, with higher rates observed in regions with poor sanitation, limited access to clean water, and inadequate food safety measures. Overall, NTS infections represent a significant public health concern, necessitating ongoing efforts in surveillance, prevention, and control strategies to mitigate their impact on global health **[74].**

Sign and Symptoms

An asymptomatic phase lasting seven to fourteen days occurs when serovar Typhi or Paratyphi A of Salmonella is consumed. Fever is the most common symptom during this time. The next week, the temperature is expected to climb and possibly reach a high plateau of 39 to 40°C. The two main symptoms are fever and rashes. Particularly high typhoid fevers can reach 104 degrees Fahrenheit, or 39 to 40 degrees Celsius, over the course of many days. Rose-colored patches, usually on the neck and belly, make up the rash, which is not always present in patients. Malaise, headaches, stomach pain, distension in the abdomen, and other constitutional symptoms are possible additional symptoms. Though diarrhea is a common symptom for many people, constipation is an earlier sign. Elevated body temperature, splenomegaly, hepatomegaly, abdominal pain, and meningism are among the physical signs. Intestinal bleeding, intestinal perforation, retention of urine, pneumonia, thrombophlebitis, myocarditis, cholecystitis, nephritis, myocarditis, osteomyelitis, and meningitis are among the major consequences **[75,76].**

Diagnosis

It is possible to identify Salmonella typhi or S. paratyphi through culture of the organism or serological procedures that involve the use of serum or urine samples. Urine, feces, bone marrow, or blood can all be used to cultivate the organism. The most reliable technique to verify typhoid fever is to isolate S. typhi from bone marrow. All typhoid fast antibody tests were shown to perform poorly when compared to blood cultures. For diagnosis, using the Widal

test in addition to S. typhi culture from stool samples. Typhoid fever is a disease of overdiagnosis and underdiagnosis in the majority of developing nations, and the most common way to diagnose S. typhi in Africa is using the serological Widal's test. Typhidot, TUBEX, and MultiTest Dip-S-Ticks are quick tests that are used to identify immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin G (IgG), respectively, in cases of typhoid fever **[77].**

Prevention and control

Typhoid fever control involves advocating for personal hygiene and implementing WASH and other measures such as a strong surveillance system for monitoring the disease burden. Early diagnosis and treatment also reduce the risk of the disease spreading from patients and other members of the community. The retrospective study conducted in India has shed light on the disease's presentation and spread, its consequences, and the patterns of antibiotic resistance. One of India's most important public health initiatives, the Integrated Disease Surveillance Programme (IDSP) is a part of the public Health Mission for All States and Union Territories. It was launched in 2004. Its primary goal is to create and improve a decentralized, computerized, laboratory-based disease surveillance system to monitor 22 diseases, including enteric fever, and to identify and react accordingly. The incidence of typhoid fever in children between the ages of six months and fifteen years will be estimated in an age-specific manner by the National Surveillance System for Enteric Fever in India (NSSEFI), a recent study conducted in India **[78].**

Antimicrobial Resistance

Chloramphenicol was adopted as the accepted antibiotic for the treatment of typhoid in 1948 **[79].** It took two years for resistance to develop, but it wasn't until 1972 that typhoid fever resistant to chloramphenicol became a significant issue. Mexico, India, Vietnam, Thailand, Korea, and Peru all saw outbreaks. These strains of S. enterica serotype typhi were also resistant to streptomycin, tetracycline, and sulfonamides; nonetheless, amoxicillin and trimethoprim–sulfamethoxazole were still viable alternative medications at first. S. enterica serotype typhi simultaneously developed resistance to all of the medications that were then used as first-line treatment (chloramphenicol, trimethoprim, sulfamethoxazole, and ampicillin) at the end of the 1980s and the beginning of the 1990s **[80].** In many parts of Asia, strains of S. enterica serotype typhi that are resistant to several drugs are still prevalent, but in other regions, bacteria that are completely resistant to all first-line antibiotics have returned **[81].**

Treatments

Antibiotics are typically used to treat typhoid fever, and research has shown that starting antimicrobial medication early on can lower the risk of complications and death as well as shorten the illness's duration. In cases where a patient has a clinical suspicion of typhoid fever but no confirmed diagnosis, doctors may nevertheless treat them with antibiotics due to the significant risk of morbidity and fatality if treatment is not received. Large surveillance studies from Asia and Africa, however, show that only 1-4% of suspected cases have typhoid that is confirmed by culture, suggesting that significant overuse of needless antibiotics may frequently occur. S. Typhi is under more selection pressure as a result of the empiric prescription of antibiotics. Since 1948, when chloramphenicol's effectiveness in treating typhoid was established, there has been a trend in the use of antibiotics and the ensuing emergence of antibiotic resistance. Consequently, with rising rates of treatment failure, antibiotic resistance has emerged as a serious concern to the management of typhoid **[82].**

Vaccination

Antibiotic medications are currently available for the treatment of typhoid fever; however, vaccination is necessary in high-risk populations for typhoid fever due to the rising rates of antibiotic resistance. As a result, Ty21a and Vi, two approved vaccinations, are advised for use by the World Health Organization (WHO) **[83].** Vi is an injectable capsular polysaccharide vaccine, and Ty21a is an oral live-attenuated vaccine. Clinical trials and outdoor settings have demonstrated the safety and effectiveness of both vaccinations **[84].**

Conclusion

Salmonella Typhimurium continues to pose a significant public health challenge due to its widespread presence in food and its capacity to cause severe illness. Its persistence and pathogenicity are driven by virulence factors that enable it to adhere to and invade host cells, survive intracellularly, and form biofilms. Recent advances in genomic and proteomic technologies have identified new targets for vaccine and antimicrobial development. Controlling S. Typhimurium infections requires a comprehensive approach that includes enhancing food safety practices, improving surveillance systems, and educating the public on proper food handling techniques. Ongoing research is vital to developing innovative interventions to reduce the global incidence of salmonellosis. By combining these strategies, we can better mitigate the impact of this pathogen on public health.

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