

A Review of Salmonellosis Infection, Modes of Transmission, and its Drugs Resistance

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Abstract: Salmonella is a common foodborne bacterium that causes both human and animal gastroenteritis. Salmonella, which includes over 2500 identified serovars, is extremely harmful. People contract Salmonella through the farm-to-fork chain, often as a result of eating animal-derived foods. Fish, non-animal-derived foods and beef, pork, including vegetables and fruits, are the next most important sources after poultry and poultry products. Salmonellosis is mainly treated with antibiotics, the growth of multidrug-resistant (MDR) Salmonella strains and an increase in antibiotic resistance have made the need to find antibiotic alternatives progressively important. The epidemiology and dynamics of transmission of the disease must be thoroughly understood in order to manage infections effectively. This comprehensive review thus focuses on the host range, transmission dynamics, risk factors, and the causes of infection of Salmonella serotypes. This study also looks at the genesis, antibiotic resistance, symptoms of the disease in humans and animals, and potential treatment and control strategies for salmonellosis, with an emphasis on the latest antibiotic-alternative infection control strategies.

Keywords: Salmonella; antibiotics; antibiotic resistance; Foodborne pathogens; antibiotic-alternatives

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Introduction

Salmonella belongs to the foodborne pathogen family Enterobacteriaceae. Among the top four causes of diarrhea in the world, Salmonella can infect humans and cause gastroenteritis. It can infect mammals, amphibians, and reptiles and spreads to healthy hosts through contaminated food or water. According to the Centers for Disease Control and Prevention (CDC), there are approximately 420 Salmonella-related deaths and 1.35 million cases of infection annually. The yearly economic cost of salmonella, which is

around \$3.3 billion, has health authorities quite concerned about the increasing antibiotic resistance of *Salmonella* spp. in recent years, which is mostly due to improper use in cattle [1]. In the United States, between February and July of 2022, there were about 884 cases of salmonella in 48 states. Poultry products are thought to be a significant source of *Salmonella* infections. Between 200 million and 1 billion cases of *Salmonella* infections are reported worldwide each year, leading to 93 million gastroenteritis cases and 155,000 fatalities; of these, approximately 85% are linked to eating tainted food [2]. *Salmonella* is classified as a category B pathogen due to its low fatality rate and moderate morbidity. Human infections can be categorized as either typhoidal or non-typhoidal, and the host's immunological state and the bacterial serotype affect how severe the infection is. Symptoms of non-typhoidal infections are common. *Salmonella* infections cause fever, cramping in the abdomen, and sudden diarrhea, while 5% of people, especially the elderly, children, and patients with weakened immune systems, may get invasive diseases like meningitis, osteomyelitis, septic arthritis, or endovascular infections caused by human pathogenic microorganisms in food. These infections pose serious and pervasive concerns, resulting in significant economic losses and negative effects on public health [3]. diseases that spread widely and are not particular and are brought on by the typhoidal *Salmonella* serovars can infect birds of any age and cause symptoms such as headache, loss of appetite, diarrhea or constipation, and a prolonged temperature (39–40°C). However, infant turkeys and chickens are especially vulnerable during the first their lives. Outbreaks of salmonellosis (SO) constitute a serious danger to developing nations' healthcare systems [4]. Vaccines are used for prevention and control human and animal *Salmonella* infections. The Food and Drug Administration (FDA) has approved two vaccines against *Salmonella*: the intramuscular Vi polysaccharide capsular vaccine and the live attenuated Ty21a oral vaccine. *Salmonella* infections are empirically treated with cephalosporins like ceftriaxone and macrolides like azithromycin due to the increasing bacterial resistance to fluoroquinolones. The significance of ongoing surveillance of *Salmonella* serotypes and antibiotic resistance in the poultry chain is underscored by research conducted in China that found a high percentage of multidrug-resistant *Salmonella* from poultry sources [5]. The fact that *Salmonella* serotypes differ widely and show significant genetic variability within and between hosts makes infection control more challenging. The epidemiology of salmonellosis is discussed in this review, with an emphasis on the etiology, host spectrum, clinical symptoms, transmission dynamics, and current outbreaks. Probiotics, prebiotics, bacteriophages, essential oils, antimicrobial peptides and vaccines are all necessary to *Salmonella* infections are controlled in both animals and humans. Globally, foodborne and waterborne illnesses and outbreaks are a neglected public health concern that must be addressed in order to lower AMR-*Salmonella* infections in both humans and animals. One of the main causes of illness in underdeveloped nations is diarrheal sickness brought on by waterborne and foodborne diseases [6].

2. Epidemiology of Salmonellosis

2.1. Salmonella Serotypes and Host Spectrum

Although the high mortality rate and low morbidity rate of *Salmonella* typhoid fever are well-known, there are over 2400 serotypes of NTS that can infect both humans and animals, mainly *S. Typhimurium*, *S. Newport*, *S. Enteritidis* and *S. Heidelberg*. Additionally, NTS can spread quickly from infected hosts and effortlessly adjust to a range of hosts by ingesting contaminated food and water. for example, Some serotypes, such as *S. Typhimurium*, *S. enterica* serovar, have been identified as the archetypal broad host range serotypes, capable of infecting domestic poultry, horses, pigeons, rodents, birds, animals, and humans. Various *Salmonella* serotypes are regarded as one of the world's most significant food pathogens [7]. To remain inside the host and avoid immune responses, they have developed ways to colonize non-phagocytic cells. Typhoid bacteria They migrate to the reticuloendothelial system from the intestines. As it spreads, it also commonly colonizes the surface of the gallstones and between 1 and 6% of *Salmonella* Typhi infections cause silent, To slow the development of salmonellosis, preventive measures and control tactics have been put in place, such as immunization programs, food safety regulations, and public health education [8].

2.2. Infection Source and Transmission Mechanism in Humans and Animals

Salmonella species are a typical part of the gut and intestinal microbiome, animals may be able to help spread the virus to people either directly or indirectly. One of the many causes of salmonella infection is including (1) poultry and chicken products, which are thought to be the main source of salmonella infections in humans. During the processing of corpses, diseased organs such as the liver and intestines are often handled improperly, resulting in contaminated meat. Both the US and Canada have declared frozen raw breaded chicken products (FRBCP) as a Salmonella threat. Additionally, Salmonella's multi-drug resistance (MDR) has sharply grown. Apart from MDR Salmonella, reports of extensively drug-resistant (XDR) and pan-drug-resistant (PDR) Salmonella have been made worldwide [9]. Among a list of 18 food items, eggs and egg products were the most common cause of salmonella outbreaks, (2) Grinded beef: A survey found that 67% of Americans prefer ground beef specifically, and 82.2% of Americans eat beef on a weekly basis. In the United States, eating beef is responsible for 10% of human salmonellosis, with 34%, 25%, and 16% of Salmonella outbreaks being caused by chicken, pig, and beef, respectively. A study conducted in Italy shows the benefits of combining data from veterinary and human health services to create predictive models of human salmonellosis incidence, which can be used to reduce the negative public health effects of foodborne illness [10]. (3) Pets who are fed a raw food diet, such as dogs, are more prone to harbor Salmonella serovars like S. Kentucky, Heidelberg, and S. Typhimurium. To promote clinical treatment and prevention, a 2018–2023 study conducted in Guangzhou, China, examined the prevalence, serotypes, and antimicrobial properties of Salmonella isolated from children [11]. (4) Both pets and humans become infected with Salmonella primarily through the consumption of contaminated meat from wild animals such as deer, wild boar, and other wild birds, or through close contact with diseased animals' tainted excrement. The disease is primarily spread by wild animals, such as feral pigs and wild boar. Epidemic data enable illnesses to be connected to specific food sources, even if the majority of Salmonella infections are sporadic (i.e., not associated with a known epidemic) [12]. (5) Insects are another vector that disperses Salmonella in agricultural settings. Research has shown that domestic waste flies and house flies can carry the following serotypes: Enteritidis, Heidelberg, and Infantis. Fifteen different serotypes of the common house fly (the domestic house fly) were also found on a pig farm. This information provided insight into possible fungal pathogens or symbionts that may affect human environments and health [13]. (6) Rodents, notably house mice, are a major source of disease on farms. The house mouse (*Mus musculus*) is reportedly one of the primary ways that farm animals get Salmonella Enteritidis. Additionally, several Salmonella serotypes have been linked to *R. norvegicus*, *R. rattus* and *M. musculus domesticus* in pig and poultry farms, and multiple studies have linked S. Enteritidis illnesses impacting species like roof rats. Humans may also get the infection from other places, Such as polluted cars, floors, and water irrigating crops with polluted water, or coming into close contact with animal excrement containing Salmonella. populations of animals and people in the same region. Salmonella multi-resistant to clinically significant antimicrobials, including fluoroquinolones and third-generation cephalosporins, has been a growing global concern in recent years [14].

2.3. Clinical Symptoms in Human and Animals

2.3.1. In Humans

Salmonella typhi strains are the cause of fever, such as S. Typhi or S. Paratyphi. sometimes known as typhoid or paratyphoid. During the incubation period, which lasts for at least a week, people with enteric fever have a variety of symptoms, such as a high temperature, vomiting, diarrhea, and headaches. In endemic areas, gastrointestinal problems impact 15% of infected people. including pancreatitis, cholecystitis, hepatitis and spleen enlargement, muscle pain, bradycardia, and pink spots on the chest and abdomen [15]. Based on the three main antigenic determinants—somatic (O), capsular (K), and flagellar (H) Salmonella is divided into serotypes. Salmonella species are serious public health threats because almost all of them are capable of infecting, replicating, and surviving in human host cells, utilizing their arsenal of pathogens and virulence factors [16].

2.3.2. In Animals

Salmonella infections can occur in both wild and domesticated animals; the bacterium usually affects the host's gastrointestinal tracts without producing any obvious symptoms. Both clinical (symptomatic) and subclinical (asymptomatic) forms of Salmonella can manifest; the clinical symptoms in hens, which can serve as healthy carriers, depend on the pathogen's serotype. This bacterium has about 2,600 serovars, most of which can infect humans through contaminated food, especially animal-based foods, especially chicken products (eggs, livers, and minced meat), as well as other meats [17]. While avian typhoid fever can cause severe diarrhea, weakness, dehydration, septicemia, and death, *S. enterica* serovar Pullorum, for example, causes anorexia, dehydration, diarrhea, and death in young chickens, as well as diarrhea, reduced egg production, and increased mortality in adult birds. Similarly, bacterial serotype and age group influence the severity of Salmonella infection in animals, especially in ruminants. Notably, NTS serotypes *S. Dublin* and *S. Typhimurium* have been directly linked to numerous reports of abortion in cattle. Bacteria are internalized either by active invasion of both phagocytic and non-phagocytic cells or by phagocytosis, which entails the ingestion of bacteria [18].

3. A number of virulence factors are necessary for *Salmonella* to invade and colonize host cells, including

3.1. Virulence Plasmid

Virulence plasmids are essential for bacteria because they contain genes linked to resistance to antibiotics and virulence factors like *spvB* (ADP-ribosylating toxin) and *spvC* (inhibits pyroptosis and inflammation). These plasmids can spread horizontally through transformation and conjugation, and they are essential for the host to develop a systemic illness. They are large and exist in small quantities to ensure dissemination and preserve their existence. Typhoid fever, which is primarily caused by *Salmonella Typhi*, can lead to serious, life-threatening complications like encephalopathy [19].

3.2. Superoxide Dismutase

A class of enzymes known as superoxide dismutase (SOD) catalyzes the transformation of superoxide radicals (O_2^-) into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). The phagosome's NADPH oxidase activity is the main cause of the reactive oxygen species produced by many host cells. *Salmonella* counteracts this effect by using SOD and the enzymes *SodCI* and *SodCII*. Consequently, the enzyme can keep working and aid the bacteria in surviving in the hostile phagosome environment [20].

3.3. Type 1 Secretion System (T1SS)

Biofilm output, adhesion, and invasion into host immune cells are regulated by the system. A related Type 1 secretion system (T1SS) carries two separate surface-associated proteins: *SiiE*, which is in charge of the first adherence to host cells, which is followed by invasion. *Salmonella*'s type 1 secretion system transports a number of substances into its extracellular space, including lipases, surface proteins, toxins, and *BapA*, which adheres to host cells and forms biofilms. They then begin to contribute to ongoing harm to epithelial cells, rendering the host asymptomatic and potentially a carrier of this pathogen for long term [21].

3.4. Type III Secretion Systems

The third secretion system (T3SS) in *Salmonella* is represented by two different pathogenic molecules, SPI1 and SPI2. SPI-1 represents the T3SS1 protein, essential for the invasion of non-phagocytic epithelial cells, while SPI-2 makes the effector T3SS2 proteins, controlling the effectiveness of the *Salmonella*-containing vacuole (SCV) membrane. T3SSs transport proteins from the bacterial cytoplasm to the host cytosol. These effector proteins cooperate to impair the host's pro-inflammatory responses, signal transduction pathways, and cytoskeleton. They also impact immunological responses, move SCVs to specific areas within host cells, and change the cytoskeleton and migration of infected cells. After 77% of samples tested positive for *Salmonella Typhi* and 70% for *Salmonella Paratyphi*, a study conducted in

Kathmandu, Nepal, identified stone waterspouts as the primary mode of transmission [22].

3.5. Fimbriae

Salmonella infection development depends critically on adherence to the host cells. FGCs, or fimbrial gene clusters, encode extracellular fimbriae and are found in the Salmonella genome. Type 1 fimbriae (T1F) are among the most prevalent sticky structures among extracellular fimbriae; T1F is composed of two main proteins, fimA and fimH, which are sticky proteins that are required to attach to particular receptors; ideally, these proteins are glycoproteins with mannose residues at the end. Pro-inflammatory cytokine expression is significantly impacted by the sticky protein fimH, a pathogen-associated molecular pattern that host TLRs identify. A phylogenetic analysis of Salmonella Typhi isolates from Hong Kong Island was conducted between 2020 and 2022. This work included whole-genome analysis to identify the dominant strain and the prevalence of antibiotic resistance genes (ARGs) [23].

3.6. Lipopolysaccharides (LPS)

The outer membrane of Gram-negative bacteria consists mainly of lipopolysaccharides (LPs). They activate the host immune response, act as a permeability barrier, and stabilize cells. They are primarily responsible for adhesion penetration of host epithelial cells; appropriate O antigen distribution is essential for *S. Typhimurium* to be highly virulent. Assessing the number of antibiotic-resistant genes and their patterns in Salmonella Typhi isolated from drinking water sources was the goal of a study conducted in Chattogram City, Bangladesh [24].

3.7. Vi Antigen

The "Vi antigen," a capsule of polysaccharides produced surface of cells by Salmonella enterica serovar Typhi, helps the bacteria become resistant to the host immune system and prevents phagocytosis while allowing them to cross the phagocyte-mediated barrier. This is how it varies from NTS. Additionally, it inhibits *S. Typhi*'s translocation to the gallbladder. At last, it inhibits IgM binding, which enables the pathogen to stop neutrophil respiratory burst, neutrophil phagocytosis, and neutrophil chemotaxis [25].

3.8. Toxins

The ability of *S. Typhi* to create toxins that cause typhoid fever is one of its most important characteristics. The receptor component (B) and the enzymatic subunit (A) are also members of the AB toxin category, which contains this typhoid toxin. Salmonella-containing vacuoles transfer the toxin from infected cells into the environment, where it can impact a larger number of target cells [26].

3.9. Flagella

Flagella are involved in protein export, adhesion, invasion, and formation of biofilm, all of which contribute to the motility of Salmonella. The transcription factor CsgD regulates the development of biofilms. The flagellin genes fljB and fliC are found in Salmonella. Bacteria with diminished flagellar mobility show less colony growth in biofilms, and fliC expression is more important than fljB expression for finding specific spots on host cells. Depending on the serotype, these pathogens can cause illnesses ranging from septicemia to diarrhea [27].

4. Antibiotics Used to Treat Antimicrobial Resistance and Salmonella

Supportive therapy is usually used to treat Salmonella infections, as the infection usually resolves on its own and the patients don't need therapeutic intervention. Previously, chloramphenicol was used to treat salmonella infections. However, people with weakened immune systems, underlying medical conditions, or severe infections may need antibiotics. Third-generation an antibiotic such as levofloxacin and ciprofloxacin, and macrolides are the most widely used antibiotics. The rate of antibiotic resistance has been enhanced by 20–30% every ten years, though the degree of resistance differs depending on the antibiotic and the bacterial serotype, underscoring the complex links between environmental factors and microbial genetic factors. A study conducted in Kirkuk examined bacteria that cause food poisoning and

diarrhea that spread orally through contaminated food and water, particularly in children [28]. Many studies have previously identified *Salmonella* that is resistant to multiple drugs. For example, it was reported that 30.9% of isolated *Salmonella* strains from broiler farms were resistant to streptomycin, 13.9% to tetracycline, 12.6% to gentamycin, and 8.6% to sulfamethoxazole-trimethoprim. Similarly, a significant level of resistance was observed towards ceftriaxone (75%) and ceftiofur (44%). For example, 17% of Egyptian broiler chickens were found to be resistant to neomycin (100%), cefoxitin and nalidixic acid (95%), cefotaxime (77.2%), norfloxacin (86.2%), amikacin (72.6%), chloramphenicol (40.8%) and erythromycin (67.8%). The cecal tonsils are the greatest location to isolate the germs, according to a study conducted in Kirkuk farms. Furthermore, *Salmonella enteritidis* was the most often identified strain of *Salmonella* in the examined samples [29].

5. Conclusions

The health of humans and animals is seriously jeopardized by salmonella and other foodborne diseases, which also cause enormous financial losses for the worldwide agriculture and healthcare sectors. The increased usage of antibiotics in animals raised for food, principally to promote development, prevention, and treatment, has led to the quick appearance and global disperse of antibiotic-resistant salmonella. In addition, the inaccurate use of antibiotics has contributed to the emergence of multidrug-resistant strains. Antimicrobial-resistant strains require an exhaustive strategy that includes early infection finding and the use of the essential biosecurity measures to allow to effectively control the outbreak within an infected individual or animal farm. Because early infection detection reduces the need for broad-spectrum antibiotics and makes it easier to begin suitable, personalised treatments on time, it reduces the selective pressure that leads to the development and spread of AMR strains in bacteria. In addition to early outbreak detection, antibiotic-alternative therapies show promise in combating AMR strains. Numerous studies have looked into alternative intervention strategies to stop the spread of AMR *Salmonella*. These include of phage therapy, antimicrobial peptides, probiotics, prebiotics, virulence quorum-sensing inhibitors, vaccines, essential oils, organic acids, and small-molecule growth inhibitors. These strategies can be used alone or in combination.

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