From Farm to Fork: The Zoonotic Transmission of Salmonella spp. and the Rise of Antimicrobial Resistance

Shameeran Salman Ismael[1,*], Bland Husamuldeen Abdullah[1] and Barhav Issa Abdullah[1]

[1]Department of Medical Laboratory Sciences, College of Health Sciences, University of Duhok, Duhok, Iraq
*Corresponding author: shameeran.Ismael@uod.ac

Abstract

Salmonella is a zoonotic foodborne bacterium that causes gastroenteritis in both humans and animals. With more than 2000 serovars known to exist, salmonella is a very dangerous bacterium. The serovars that produce typhoid fever are known as non-typhoidal *Salmonella*, and they are responsible for both gastroenteritis and the illness. Eating foods from animals is often linked to Salmonella infection, which humans can get through the farm-to-fork chain. The next most significant sources, after poultry products, are fish, cattle, pork products, vegetables, and fruit. The rise of antimicrobial resistance and the introduction of resistant strains of Salmonella to multiple drugs have made identifying antibiotic alternatives more urgent, even though antibiotics are still the main treatment for salmonellosis. Many virulence factors are required to adhere to, invade, and evade the host's defense system. Salmonella's pathogenicity, including its adhesion proteins, flagella, plasmids, type 3 secretion systems, and capsule. According to the recent rise in the presence of NTS variants worldwide, control methods meant to reduce food animal contaminants throughout the food chain might not have been successful. The emergence of antibiotic-resistant Salmonella bacteria also raises the possibility of a food safety emergency. Thus, the spread of Salmonellosis and the emergence of outbreaks of antibiotic resistance were the main topics of this chapter.

Keywords: Salmonellosis, Zoonosis, Antimicrobial resistance, Farm, Food

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Introduction

Salmonellosis is the most prevalent zoonotic foodborne bacteria and a global public health concern. With more than 2000 serovars, *Salmonella enterica* is the most virulent species. It causes gastroenteritis and typhoid fever, and the serovars that cause the latter are called non-typhoidal Salmonella (Somorin et al., 2021). *Salmonella* is under the family Enterobacteriaceae. It can live in mammals, amphibians, and reptiles and causes gastroenteritis in humans (Sánchez-Vargas et al., 2011; CDC, 2023). Through the farm-to-fork chain, Salmonella gets spread to people and is frequently associated with eating foods derived from animals. Chicken and chicken products are the main contributors among these sources, followed by red meat, pig meat, fish meat, vegetables, and fruits (Lamichhane et al., 2024). *Salmonella* is listed by the World Health Organization as one of the top four global causes of diarrhea (Hoffmann et al., 2012, Chlebicz & Śliżewska, 2018).

The bacterial serotype and the host's immune system determine the severity of the two types of human infections: typhoidal and non-typhoidal (Wei et al., 2023). Fever, cramping in the abdomen, and diarrhea with an abrupt onset are common symptoms of non-typhoidal Salmonella infections (Keestra-Gounder et al., 2015). It typically resolves on its own in one to seven days without therapy, depending on the host (Hoelzer et al., 2011). However, 5% of individuals, particularly those with weakened immune systems, newborns, and the elderly, may get bacterial infections or invasive infections such as septic arthritis, meningitis and osteomyelitis, and endovascular infections (Olnood et al., 2015, Wibisono et al., 2020).

Clinical problems in highly vulnerable people are typically treated with broad-spectrum antibiotics (Galán, 2021). The earliest antibiotics used to treat salmonellosis were trimethoprim/sulfamethoxazole and chloramphenicol (Stoycheva & Murdjeva, 2006). The third generation of quinolones, such as fluoroquinolones, ofloxacin, and ciprofloxacin, is currently the medication for salmonellosis in individuals with weakened immune systems (Jibril et al., 2021). Ceftriaxone and azithromycin are used empirically to treat salmonellosis because of the growing bacterial resistance to fluoroquinolones (Hailu et al., 2021).

Vaccines, like medicine, were used for the prevention of salmonellosis in humans and animals (van Panhuis et al., 2013). The Food and Drug Administration has approved two vaccines to prevent Salmonella: the oral live attenuated Ty21a vaccine and the intramuscular Vi polysaccharide capsular vaccine. New attenuated vaccines, glycoconjugate, O-antigen glycoconjugate, and GMMA-based vaccines are still being developed (Sears et al., 2021). The effectiveness of immunizations against Salmonella is limited by a number of reasons, including complex immune evasion mechanisms, a range of serotypes, and the presence of asymptomatic carriers, making vaccine design difficult (Giannelli et al., 2017). This chapter aimed to determine the transmission of Salmonella spp. and the rise of antimicrobial resistance outbreaks

Transmission of Salmonellosis

Since chicken is believed to be the primary cause of *Salmonella* infection in humans, poultry as well as poultry goods are the initial point of infection (Gonzalez-Escobedo & Gunn, 2013). Incorrect handling of contaminated organs, such as the stomach and liver, during carcass processing is the most frequent cause of contaminated meat (*Dos Santos et al., 2020*). The second source is ground meat, 82.2% of Americans eat beef every week, with 67% specifically stating that they prefer ground beef meat (CDC, 2023). Worldwide, domesticated animals and people are mostly exposed to *Salmonella* through wild animals, such as feral pigs and wild boar (Cilia et al., 2021). Humans are usually infected by eating contaminated meat from poultry as well as wild animals, or by coming into close contact with contaminated animal excrement (Gil Molino et al., 2019).

Almost all of the Salmonella-related infections that occur globally each year are foodborne; the infection can be transferred by either indirect or direct contact within the household, at the hospital, or on a farm (Majowicz et al., 2010). *Salmonella* can spread by direct contact, such as when feces-contaminated food or drink is consumed (Ford et al., 2023). Vertical transmission typically occurs in birds and reptiles when pollen via the female reproductive system can reach the eggs (*Griffith et al., 2019*). By employing intermediary objects such as infected tools and live or dead vectors, the germs can spread indirectly (Dróżdż et al., 2021). Figure 1 highlights the transmission of salmonellosis.

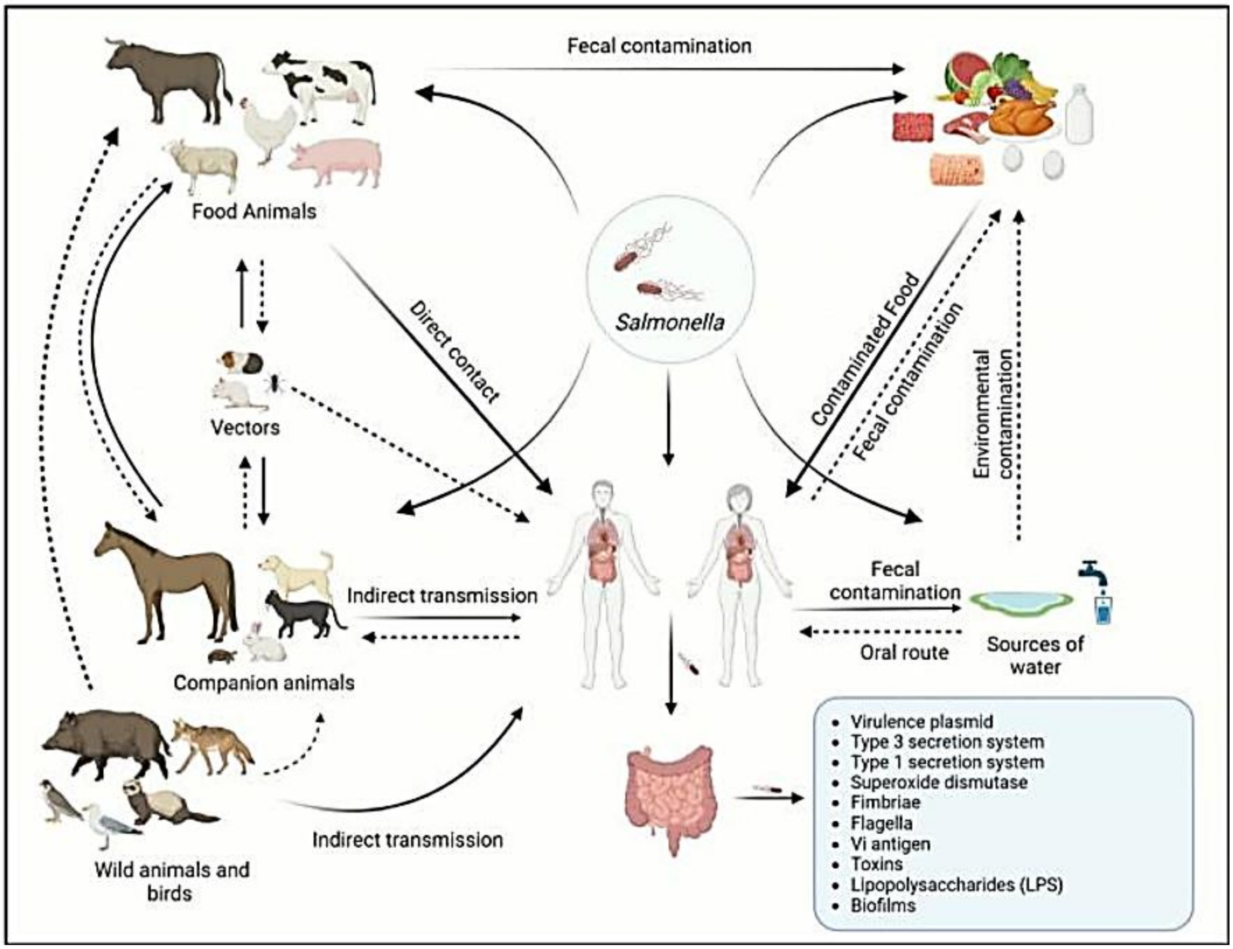

Fig. 1: Routes of transmission of salmonellosis in humans and animals (Lamichhane et al., 2024) https://pmc.ncbi.nlm.nih.gov/articles/PMC10812683/

Clinical Signs of Salmonellosis

There are two common types of salmonellosis typhoidal and non-typhoidal

Typhoidal or Enteric Fever

Commonly referred to as typhoid or paratyphoid, it is caused by typhoidal *Salmonella* serovars, such as *Salmonella typhi* or *Salmonella paratyphi* (Reddy et al., 2010) A week or more is the incubation period for enteric fever, during which time people may found with several symptoms, including a high fever, headache, vomiting, and diarrhea A noticeable temperature pattern appears during enteric fever (Crump, 2019). In the first week, it starts as a low-grade fever ranging between 37.5°C to 38°C, and then progressively increases to a high-grade fever (41.5°C) (Thakur et al., 2022). If proper treatment is not received, the fever may last up to one month (Patel et al., 2010). Infected people may have bradycardia, myalgia, splenomegaly, hepatomegaly, and the appearance of red on the abdomen and chest in addition to fever (Kuvandik et al., 2009). Hepatitis, pancreatitis, and cholecystitis are among the common gastrointestinal problems that affect about 15% of infected individuals with salmonellosis in endemic areas (Galán, 2016). Bloody diarrhea, or eruption of Peyer's patches, is lymphatic nodules in the last part of the ileum that can result in hemorrhage, one of the most dangerous gastrointestinal adverse effects (Crump, 2019).

Non Typhoidal Salmonellosis

The most common causative agents for this type of infection are *Salmonella typhimurium, Salmonella* enteritidis, and *Salmonella newport* (Bakhshandeh et al., 2022). The infection typically lasts 4–7 days, with an incubation period ranging from 6 hours to a week following the initial inoculation (Pulford et al., 2021). Gastroenteritis is the most prevalent symptom in humans, with clinical manifestations such as nausea, vomiting, abdominal pain, diarrhea, and muscle soreness (Hohmann, 2001). The severity of the infections increases, among immunocompromised patients, elderly immunocompromised adults, and newborns and toddlers under five years of age (Scallan et al., 2011). Cholecystitis, pancreatitis, and appendicitis are among the disorders that might appear and worsen, eventually developing into meningitis and sepsis, which are life-threatening. Dehydration, which can be fatal in babies and older individuals, can result from inadequate fluid balance brought on by a protracted loss of body fluids (Schempp et al., 2019, Ehuwa et al., 2021).

Pathogenesis of Salmonellosis

Salmonellosis is more likely to affect the elderly, young children (less than five years old), and people with immunocompromised patients. *Salmonella* exhibited a peculiar trait during its colonization of non-phagocytic cells (Crump, 2019), whereby it initiates phagocytosis in order to gain entry into the host cell. The *Salmonella* pathogenicity islands (SPIs), a group of genes located in a vast section of the chromosome DNA and representing the structural domains that take part in the invasion process, contain these virulence factors (Grassl & Finlay, 2008). After entering the digestive system by tainted food or drink, the bacteria tend to pierce the intestinal wall epithelial cells. The specialized microfold cells found in the lymphoid tissue, commonly known as Peyer's patches (Dillon & Lo, 2019), or the active penetration of nonphagocytic cells through the so-called "trigger" process (Roche et al., 2018) are the primary mechanisms by which *Salmonella* is transported across the intestinal barrier (Dos Santos et al., 2020).

Salmonella's pathogenicity depends on its intracellular persistence, which can differ across strains with high and low virulence (Choi et al., 2019, Pradhan & Negi, 2019). A host-derived membrane sheath called a vacuole also referred to as a *Salmonella*-containing vacuole, or SCV envelops the bacterium upon engulfment. After the phagosome and lysosome fuse, the host cell releases reactive oxygen species and enzymes to eliminate the bacteria it has acquired (Villanueva et al., 2022). The bacterium uses the T3SS to inject effector proteins straight into the vacuole, changing the structure of the compartment. In order to safeguard the organism in the intracellular niche and facilitate safe reproduction, the altered vacuole shape prevents phagolysosomal fusion (Reddy et al., 2010). A noticeable temperature pattern appears during enteric fever (Thakur et al., 2022). If proper treatment is not received, the fever may last up to one month (Patel et al., 2010). Infected people may have bradycardia, myalgia, splenomegaly, hepatomegaly, and the appearance of red on the abdomen and chest in addition to fever (Kuvandik et al., 2009). Hepatitis, pancreatitis, and cholecystitis (Galán, 2016).

Virulent Factors

There are several virulent factors associated with the pathogenesis of salmonellosis such as:

1. Virulence plasmids are essential for bacteria because they contain genes linked to virulence factors like spvB (ADP-ribosylating toxin) spvC (inhibits inflammation and pyroptosis) and antibiotic resistance (Zuo et al., 2020, Mellor et al., 2022). These plasmids can transmit horizontal gene transfer by transformation and conjugation (Rodríguez-Beltrán et al., 2021). To avoid being retained throughout cell division, they are big and present in small quantities to reduce the burden on the host's cell metabolism (Sengupta & Austin, 2011).
2. *Salmonella's* extracellular area is supplied with a variety of substances, including toxins, surface proteins, lipases, and adenylate cyclase, by the Type 3 secretion system (Li et al., 2019). Many plant and animal Gram-negative pathogens have complex syringe-like nanomachines called type-3 secretion systems (Kosarewicz et al., 2012).
3. There are two separate pathogenicity islands, SPI1 and SPI2, encode the T3SS in *Salmonella* (Srikanth et al., 201l). SPI-1, which encodes the T3SS1, is necessary for invasive non-phagocytic epithelia (McGhie et al., 2009, LaRock et al., 2015). The T3SS2 effector proteins, which are encoded by SPI-2, control the kinetics of *Salmonella*-containing vacuole membranes, locate SCVs in certain areas inside host cells, affect immunological responses, alter the cytoskeleton, and affect infected cell motility (Sellin et al., 2014).
4. The enzyme superoxide dismutase (SOD) is essential for preserving the cells' redox potential. One very important job of this substance is to protect healthy cells from the reactive oxygen species that are made when many intracellular pathogens infect cells (Felmy et al., 2013, Tang et al., 2022). Through their ability to intercept reactive oxygen species generated by the host's natural immune system, both enzymes are believed to contribute to Salmonella pathogenicity (Krishnakumar et al., 2007, Wang et al., 2020).
5. Among the most crucial elements of Salmonella attachment is fimbriae. Three different assembly pathways chaperon–usher, nucleation–precipitation, and type IV fimbriae are used to assemble Salmonella fimbriae. Several kinds of fimbriae result from these assembly processes. To start adhesion, *Salmonella* fimbriae attach to receptors on host cells (Grzymajło et al., 2013, Kolenda et al., 2019, Rehman et al., 2019, Uchiya et al., 2019).
6. More than 20 distinct proteins come together to form the intricate mechanism that is the bacterial flagellum (Wang et al., 2020). Although the flagellum has historically solely been thought of as a mobility organelle, it has lately become clear that flagella serve a variety of additional biological purposes (Haiko & Westerlund-Wikström, 2013; Horstmann et al., 2017; Sokaribo et al., 2020).
7. "Vi antigen," a capsular polysaccharide produced by *Salmonella enterica serovar Typhi*, is made up of residues of nonstoichiometrically O-acetylated α-1,4-linked N-acetylgalactosaminuronic acid. Current vaccinations contain this glycoprotein (Hiyoshi et al., 2018).
8. A crucial component of *Salmonella Typhi's* pathogenicity, which causes typhoid fever in humans, is typhoid toxin (Liston et al., 2016). The peculiar biology of this toxin is that Salmonella Typhi only produces it when it is within host cells. After being produced, the toxin is released into the lumen of the vacuole which contains *Salmonella*, where vesicle carrier intermediates carry it to the extracellular area (Chong et al., 2017).

9. Asymmetric lipid bilayers made up of outer leaflet lipopolysaccharides and inner leaflet phospholipids make up Gram-negative bacteria's outer membrane (OM) (Needham & Trent, 2013). Lipid A, O-antigen polysaccharide (O-PS), and core oligosaccharide (C-OS) comprise LPS (Kong et al., 2011). Additionally, LPS is in charge of host epithelial adhesion or invasion (Richards et al., 2010, Baptista et al., 2023).
10. The ability to produce biofilms and the capacity to induce acute, latent, or chronic disease are traits shared by many Salmonella species (Römling, 2005, Ismael et al., 2024). The adaptive response known as biofilms has the potential to modify bacterial gene expression, hence enhancing resistance to environmental stresses and drugs (Kader et al., 2006, Chen et al., 2012). The secretion of a polymeric matrix that is defined by the expression of several elements, including the two main components, cellulose and curli fimbriae, forms a *Salmonella* biofilm (Sanad et al., 2016).

Antibiotic Resistance to Salmonellosis

Recently, *Salmonella typhimurium* has developed multidrug resistance, rendering it untreatable with conventional antibiotics and potentially leading to deadly infections. In contrast to *Salmonella enterica* serovar *Typhimurium* LT2, *Salmonella enterica* serovar *Typhimurium* DT104 showed multidrug resistance to the antibiotic's chloramphenicol, ampicillin, tetracycline, florfenicol, streptomycin, and sulfonamides using a gene identified in *Salmonella* genomic island I (Al-Saeed et al., 2023, Abdullah et al., 2024).

Concern about antimicrobial resistance in salmonella (1,4,[5],12: -:-) has grown over the last 20 years, especially in multidrug-resistant isolates (MDR) (Vestergaard et al., 2016, Proroga et al., 2019, Qin et al., 2022). These MDR strains have an association with the rising prevalence of human salmonellosis (Mu et al., 2022, Wei et al., 2023). There are two dominant clonal lineages of salmonella multidrug resistance (1,4,[5],12: i:-:) are a European clone with an ASSuT (ampicillin, streptomycin, sulfonamides, and tetracycline) resistance pattern (Zeng et al., 2021; Keestra-Gounder et al., 2015). Salmonella (1,4,[5],12: i:-) isolates mostly from clinical sources had a high MDR rate (86.0%) in a meta-analysis (Hopkins et al., 2010; Nadimpalli et al., 2019). *Salmonella* (1,4,[5],12: i:-) isolates have also been found to be resistant to colistin, quinolones, and extended-spectrum β-lactamases (ESBLs) (García et al., 2011, Casas et al., 2016). Cleaning and sanitation practices, routine food handler screening and diagnosis, routine animal monitoring for potential carriers, and treatment of carriers and symptomatic individuals are some of these safeguards (Mancini et al., 2021, AlFaleh et al., 2023). An animal Salmonellosis needs a regular check for Salmonella infection should be conducted throughout all stages of the animal production chain (Ismael et al., 2023).

Conclusion

This chapter illustrated how Salmonella can occasionally contaminate food along the farm-to-fork chain and showed how healthy hens can harbor harmful and resistant forms of the bacteria. *Salmonella enterica* serovar is a newly discovered pathogen that can cause foodborne illnesses, especially when it contaminates foods that come from animals. New compounds and therapeutic targets that can treat *Salmonella* infections and prevent the emergence of antibiotic resistance may be found with the aid of modern technology and molecular techniques. It is essential to increase the monitoring of food isolates obtained from animals in order to curtail and control the transmission of them throughout the food chain.

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