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Accepted: 28/05/2024

Published: 30/06/2024

## Tackling salmonellosis: A comprehensive exploration of risks factors, impacts, and solutions

Siti Rani Ayuti<sup>1,2,3</sup> , Aswin Rafif Khairullah<sup>4</sup> , Mohammad Anam Al-Arif<sup>5</sup> , Mirni Lamid<sup>5\*</sup> , Sunaryo Hadi Warsito<sup>5</sup> , Ikechukwu Benjamin Moses<sup>6</sup> , Intan Permatasari Hermawan<sup>7</sup> , Otto Sahat Martua Silaen<sup>8</sup> , Widya Paramita Lokapimasari<sup>5</sup> , Suhita Aryaloka<sup>9</sup> , Teuku Reza Ferasyi<sup>2,10</sup> , Abdullah Hasib<sup>11</sup> , and Mira Delima<sup>12</sup> 

<sup>1</sup>Doctoral Program of Veterinary Science, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>2</sup>Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

<sup>3</sup>Research Center of Aceh Cattle and Local Livestock, Faculty of Agriculture, Universitas Syiah Kuala, Banda Aceh, Indonesia

<sup>4</sup>Research Center for Veterinary Science, National Research and Innovation Agency (BRIN), Bogor, Indonesia

<sup>5</sup>Division of Animal Husbandry, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>6</sup>Department of Applied Microbiology, Faculty of Science, Ebonyi State University, Abakaliki, Nigeria

<sup>7</sup>Faculty of Veterinary Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia

<sup>8</sup>Doctoral Program in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

<sup>9</sup>Master Program of Veterinary Agribusiness, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>10</sup>Center for Tropical Veterinary Studies-One Health Collaboration Center, Universitas Syiah Kuala, Banda Aceh, Indonesia

<sup>11</sup>School of Agriculture and Food Sustainability, The University of Queensland, Gatton, Australia

<sup>12</sup>Department of Animal Husbandry, Faculty of Agriculture, Universitas Syiah Kuala, Banda Aceh, Indonesia

### Abstract

Salmonellosis, caused by *Salmonella* species, is one of the most common foodborne illnesses worldwide with an estimated 93.8 million cases and about 155,000 fatalities. In both industrialized and developing nations, Salmonellosis has been reported to be one of the most prevalent foodborne zoonoses and is linked with arrays of illness syndromes such as acute and chronic enteritis, and septicemia. The two major and most common *Salmonella* species implicated in both warm-blooded and cold-blooded animals are *Salmonella bongori* and *Salmonella enterica*. To date, more than 2400 *S. enterica* serovars which affect both humans and animals have been identified. *Salmonella* is further classified into serotypes based on three primary antigenic determinants: somatic (O), flagella (H), and capsular (K). The capacity of nearly all *Salmonella* species to infect, multiply, and survive in human host cells with the aid of their pathogenic and virulence arsenals makes them deadly and important public health pathogens. Primarily, food-producing animals such as poultry, swine, cattle, and their products have been identified as important sources of salmonellosis. Additionally, raw fruits and vegetables are among other food types that have been linked to the spread of *Salmonella* spp. Based on the clinical manifestation of human salmonellosis, *Salmonella* strains can be categorized as either non-typhoidal *Salmonella* (NTS) and typhoidal *Salmonella*. The detection of aseptically collected *Salmonella* in necropsies, environmental samples, feedstuffs, rectal swabs, and food products serves as the basis for diagnosis. In developing nations, typhoid fever due to *Salmonella* Typhi typically results in the death of 5%–30% of those affected. The World Health Organization (WHO) calculated that there are between 16 and 17 million typhoid cases worldwide each year, with scarring 600,000 deaths as a result. The contagiousness of a *Salmonella* outbreak depends on the bacterial strain, serovar, growth environment, and host susceptibility. Risk factors for *Salmonella* infection include a variety of foods; for example, contaminated chicken, beef, and pork. Globally, there is a growing incidence and emergence of life-threatening clinical cases, especially due to multidrug-resistant (MDR) *Salmonella* spp, including strains exhibiting resistance to important antimicrobials such as beta-lactams, fluoroquinolones, and third-generation cephalosporins. In extreme cases, especially in situations involving very difficult-to-treat strains, death usually results. The severity of the infections resulting from *Salmonella* pathogens is dependent on the serovar type, host susceptibility, the type of bacterial strains, and growth environment. This

\*Corresponding Author: Mirni Lamid. Division of Animal Husbandry, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: [mirnylamid@fkh.unair.ac.id](mailto:mirnylamid@fkh.unair.ac.id)

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review therefore aims to detail the nomenclature, etiology, history, pathogenesis, reservoir, clinical manifestations, diagnosis, epidemiology, transmission, risk factors, antimicrobial resistance, public health importance, economic impact, treatment, and control of salmonellosis.

**Keywords:** Food, *Salmonella*, Salmonellosis, Multidrug resistance, Public health.

### Introduction

The epidemic of foodborne illnesses, which causes significant costs for people, the food sector, and the economy, highlights the continued importance of food safety (Hussain and Dawson, 2013). Although, there has been some noticeable progress in food science and technology, foodborne illnesses continue to have grave public health consequences (Elbehiry et al., 2023). The chance of contracting a foodborne illness has increased significantly over the last 20 years, putting approximately 25% of the population at higher risk (Grace, 2015). One of the most common foodborne bacterial pathogens worldwide is *Salmonella* spp, which is thought to cause 93.8 million cases of salmonellosis annually, along with 155,000 fatalities (Galán-Relaño et al., 2023).

The most common indication of a *Salmonella* infection worldwide is gastroenteritis, which is followed by bacteraemia and enteric fever (Teklemariam et al., 2023). Even though the majority of instances are minor and occasionally go away on their own, life-threatening clinical diseases are frequent. This illness has the ability to kill numerous animal species as well as people and cause both acute and chronic diarrhoea (Zha et al., 2019). Salmonellosis is thought to be the most prevalent foodborne zoonosis in both industrialized and developing nations (Galán-Relaño et al., 2023). It is also linked to numerous other illness syndromes, such as septicemia, acute, and chronic enteritis (Gal-Mor et al., 2014). Salmonellosis severity varies based on the host's age, health, and the particular strain that caused the infection (Kurtz et al., 2017).

*Salmonella* is a facultative anaerobe, rod-shaped, Gram-negative, flagellated bacterium that belongs to the Enterobacteriaceae family (Ong et al., 2013). Its dimensions are about  $2-3 \times 0.4-0.6 \mu\text{m}$ . The genus *Salmonella* has two species: *Salmonella bongori* and *Salmonella enterica* (Oludairo et al., 2013). Human outbreaks of salmonellosis are thought to be mostly caused by *S. enterica* (Teklemariam et al., 2023). More than 2400 *S. enterica* serovars have been identified to date and many of these serovars can infect both people and animals with disease (Fjelkner et al., 2023). It is believed that swine, poultry, and cattle are the primary sources of *Salmonella* (Shaji et al., 2023). This bacterial colonization occurs in the intestinal tract, skin, and feathers so it can cause clinical disease and cause significant economic losses due to infected birds and medical costs for poultry farmers (Kabir, 2010).

Antimicrobial resistance (AMR) in foodborne pathogens, such as *Salmonella*, has been associated

in the recent past with an increase in the number of deaths, extended hospital stays, and increased medical costs due to treatment failure (Rafiq et al., 2022). The prevalence of multidrug-resistant (MDR) *Salmonella* clones in humans, domestic animals, and other wildlife species has dramatically increased since these clones first appeared in the late 1990s and early 2000s (Britto et al., 2019). Globally, there is growing concern over the rising incidence of MDR *Salmonella*. This includes resistance to fluoroquinolones and third-generation cephalosporins, two therapeutically relevant antimicrobials (Marchello et al., 2020).

Contact with diseased animals or contaminated settings, as well as ingestion of contaminated animal goods, are common ways to contract *Salmonella* infections (Ehuwa et al., 2021). The most common sources of isolation for these bacteria are eggs, meat, and dairy products (Eng et al., 2015). Raw fruits and vegetables are among the other foods linked to the spread of *Salmonella* (Mkangara, 2023). The main way that this pathogen spreads is through the trafficking of animals and raw animal foods. One of the main ways that *Salmonella* can contaminate organs and carcasses is during the food animal slaughter process at slaughterhouses (Zeng et al., 2021). The public is increasingly concerned about the advent of antibiotic-resistant foodborne bacteria since they are more virulent and cause a higher death rate among sick people.

*Salmonella* infections continue to be a major global public health concern. The financial burden of both industrialized and developing countries is increased by the costs associated with disease prevention, surveillance, and treatment (Martin et al., 2023).

*Salmonella* spp. have been implicated in series of acute and chronic diarrhoea in animal species as well as human beings. Sometimes, salmonellosis might present as a minor medical condition and infected people could normally heal and get better. However, the emergence and increasing spread of MDR strains of *Salmonella* have become a major global health concern that requires very careful and prudent use of antimicrobials. Salmonellosis can be prevented and controlled by the food industry through the implementation of good manufacturing practices and strict adoption of the hazard analysis critical control point (HACCP) principle in food production processing, packaging, and storage.

Host variables noted to determine infection/disease progression include age, underlying illness, and immunological weakness or digestive tract health. The epidemiology of foodborne illnesses, especially due to bacterial pathogens, including the MDR strains has

been widely reported to cause significant economic consequences for people, the food sector, and thus, needs urgent attention and intervention. Foodborne illnesses due to MDR *Salmonella* spp have been linked to extended hospital stays, increased medical costs due to treatment failure, and an increase in the number of deaths. In fact, the financial burden of both developed and developing countries is increased by the costs associated with disease surveillance, prevention, and treatment. This review therefore aims to comprehensively detail the nomenclature, etiology, history, pathogenesis, reservoir, clinical manifestations, diagnosis, epidemiology, transmission, risk factors, AMR, public health importance, economic impact, treatment, and control of salmonellosis.

#### Nomenclature

Six subspecies of *S. enterica* have been identified based on biochemical traits and genomic relatedness. Subspecies in this nomenclature are denoted by Roman numerals by Kauffmann-White including *S. enterica* subspecies *enterica* (I); *S. enterica* subspecies *salamae* (II); *S. enterica* subspecies *arizonae* (IIIa); *S. enterica* subspecies *diarizonae* (IIIb); *S. enterica* subspecies *houtenae* (IV); and *S. enterica* subspecies *indica* (VI) (Porwollik et al., 2004). The most common subspecies of *Salmonella*, *S. enterica* subspecies *enterica* (I), is primarily associated with mammals and is responsible for 99% of infections in warm-blooded animals and humans (Teklemariam et al., 2023). Conversely, the remaining five subspecies of *S. enterica* and *S. bongori* are primarily found in cold-blooded animals and the environment and are rarely detected in humans (Waldner et al., 2012).

Apart from phylogenetic subspecies categorization, there is also the Kauffman and White classification scheme (Table 1). *Salmonella* is further divided into serotypes according to three main antigenic determinants: capsule (K), somatic (O), and flagella (H) (Rai and Mitchell, 2020). The outer membrane of bacterial cells contains the heat-stable somatic antigen (O), which is the oligosaccharide component of the lipopolysaccharide (LPS) of the cells (Whitfield et al., 2020). Multiple O antigens can be expressed by a particular serotype of *Salmonella*. The heat-stable H

antigen, which is mostly present on bacterial flagella, is involved in the host immune response's activation (Hajam et al., 2017). The genes that code for flagella proteins are found in two distinct types of *Salmonella*. These bacteria have the unusual capacity to express only one protein at a time if they are diphasic (phases I and II) (McQuiston et al., 2008).

Many serotypes express the phase I H antigens that determine immunological identification, whereas many other serotypes express the non-specific phase II antigens (Wang et al., 2020). Surface K antigen is a heat-sensitive polysaccharide that is mostly found on the surface of the bacterial capsule and is uncommon among the majority of *Salmonella* serotypes. Only the serotypes Dublin, Typhi, and Paratyphi C have the virulence antigen (Vi), the K antigen subtype (Zghair et al., 2022).

The term “serovar,” which is equivalent to “serotype,” has been used frequently in literature (Ferrari et al., 2019). Subspecies are typically left out when designating specific *Salmonella* serotypes. For instance, the enterica serotype of *S. enterica* subspecies Typhi is sometimes abbreviated in literary works as *Salmonella* ser. typhi or *S. typhi*. More than 2,400 serotypes have been found to date, with over 50% of these serotypes belonging to the *S. enterica* subspecies (Reen et al., 2005). Each serotype is distinguished by its own mix of somatic and flagellar O antigens, H1 and H2.

#### Etiology

A member of the Enterobacteriaceae family is *Salmonella*. This rod-shaped microbe (Fig. 1) is motile because it has peritrichous flagella, is a facultative anaerobe, does not make spores, and tests negative for Gram's staining and oxidase (Andino and Hanning, 2015). *Salmonella* species are roughly 2–3 × 0.4–0.6 µm in size. The majority of *Salmonella* serovars are aerogenic, with the exception of *Salmonella* serovar Typhimurium, which does not produce gas (Shaji et al., 2023). Normally, *Salmonella* converts nitrates to nitrites, produces hydrogen sulfide, and breaks down D-glucose to create hydrogen and carbon dioxide (Mendes et al., 2021). Tests for the synthesis of urease and indole (tryptophanase) have also shown negative results for *Salmonella* (Cosby et al., 2015).

Table 1. Kauffmann-White scheme's *Salmonella*.

Salmonella subspecies	Number of serotypes	Host
<i>S. enterica</i> subspecies <i>indica</i> (VI)	12	Cold-blooded animals
<i>S. bongori</i> (V)	20	Cold-blooded animals
<i>S. enterica</i> subspecies <i>houtenae</i> (IV)	70	Cold-blooded animals
<i>S. enterica</i> subspecies <i>arizonae</i> (IIIa)	94	Cold-blooded animals
<i>S. enterica</i> subspecies <i>diarizonae</i> (IIIb)	324	Cold-blooded animals
<i>S. enterica</i> subspecies <i>salamae</i> (II)	489	Cold-blooded animals
<i>S. enterica</i> subspecies <i>enterica</i> (I)	1,454	Warm-blooded animals
Total	2,463	



**Fig. 1.** Micrograph of *Salmonella* bacteria (Source: Sherris Medical Microbiology (4<sup>th</sup> edition), McGraw Hill publishers (2003)).

*Salmonella*'s 16S rDNA gene sequence study places it in the Gamma proteobacteria class (Větrovský and Baldrian, 2013).

*Salmonella* cell walls are made up of proteins, lipoproteins, lipids, and LPSs (Cestero *et al.*, 2021). The biological effects of bacteria are caused by endotoxins, which are found in LPSs and the lipid portion of the cell wall (Maldonado *et al.*, 2016). Somatic O antigens are another name for the common central polysaccharide and monosaccharide endotoxin (Kubler-Kielb *et al.*, 2013). The polymer moiety on the surface of bacteria, known as the somatic O antigen, is made up of many short oligosaccharides (Whitfield *et al.*, 2020). There are about 60 somatic antigens in *Salmonella* (Alessiani *et al.*, 2023). Genotype analysis demonstrates how genes are transferred between different types of bacteria to acquire antigens. The numbers correspond to these antigens. Using specific antisera, *Salmonella* can be categorized into multiple groups based on these somatic antigens (Robertson *et al.*, 2018).

*Salmonella* possesses the flagella antigen H as well. These are denoted by numbers and letters. Approximately 114 H antigens have been identified (McQuiston *et al.*, 2011). Heat-labile proteins make up the flagella H antigen. There are two phases to them: phases I and II of the H antigen are the terms for the specific and non-specific phases (Schreiber *et al.*, 2015). On the surface of the K antigen, certain strains of *Salmonella* generate carbohydrates that are susceptible to heat (Pearson *et al.*, 2020). Aside from that, the cell walls of *Salmonella typhi* are covered in capsular antigens, which confer pathogenicity (Jahan *et al.*, 2022). In 2,000, roughly 2,463 serotypes were described based on somatic and flagellar agglutination reactions; in 2017, it was stated that the number had increased to 3,000 (Popa and Papa, 2021).

*Salmonella* grows readily on xylose lysine deoxycholate agar, Blood agar (BA), MacConkey Agar (MCA), Salmonella-Shigella Agar, and Bismuth Sulfate Agar (Paniel and Noguier, 2019). Mannose and glucose are fermented by the bacteria on this agar, but not lactose or sucrose (Agbankpe *et al.*, 2019). *Salmonella* serotypes grow best in temperatures between 35°C and 40°C. Depending on the growth substrate and serovar involved, the bacterium can grow in a temperature range of 2°C–54°C (Keerthirathne *et al.*, 2016). Low temperatures are insufficient for *Salmonella* to flourish. The robust nature of microbes means that freezing does not necessarily have a negative impact on them (Morey and Singh, 2012). The majority of *Salmonella* serovars can withstand drying out and thrive in acidic environments with a pH of 1–4. This bacterium can withstand heat, alcohol, and weak acids (Foley *et al.*, 2013).

#### History

Early 19<sup>th</sup>-century research on *Salmonella* was carried out by Eberth, who identified the microorganism and Gaffky, who isolated the bacillus that causes typhoid illness in humans (Marineli *et al.*, 2013). Following that, *Salmonella* was found and isolated in 1885 by Theobald Smith and Daniel Elmer Salmon from the intestines of pigs afflicted with typical swine sickness (hog cholera) (Chang *et al.*, 2021). At the time, they believed that bacterium was the swine cholera's causative agent. *Salmonella* was the eventual name given to the bacterial strain in honor of Dr. Daniel Elmer Salmon, an American pathologist who collaborated closely with Smith (Kazmi, 2022). The name of the genus *Salmonella* has grown more complex and contentious in recent years, and it is still up for discussion. Presently, the World Health Organization's (WHO) suggested *Salmonella* nomenclature scheme is used by the majority of *Salmonella* reference centers worldwide, including the Centers for Disease Control and Prevention (Brenner *et al.*, 2000). *Salmonella* is divided into two species under this nomenclature system according to variations in 16S rRNA sequencing analysis (Větrovský and Baldrian, 2013). These two common species are *S. bongori* and *S. enterica*.

#### Pathogenesis

The severity of a human *Salmonella* infection varies according to the patient's health and serotype. Older people, small children, and those with compromised immune systems are more susceptible to contracting *Salmonella* infections than the general public (Ehuwa *et al.*, 2021). The capacity of nearly all *Salmonella* strains to infect, multiply, and survive in human host cells makes them dangerous and possibly deadly (Kurtz *et al.*, 2017). The fact that *Salmonella* initiates its own phagocytosis in order to infiltrate the host cells is an intriguing aspect of its invasion of human non-phagocytic host cells (Mambu *et al.*, 2017). The *Salmonella* Pathogenicity Island (SPI), a collection of genes spread throughout a substantial stretch of chromosomal DNA that code for

structures crucial in the invasion process, provided the remarkable genetics underpinning this cunning tactic (Lerminiaux *et al.*, 2020). Bacteria typically infiltrate the intestinal wall's epithelial cells when they enter the digestive system through tainted food or water (Fàbrega and Vila, 2013). *Salmonella* uses the type III secretion system, a multichannel protein that is encoded by SPI, to inject its effectors into the cytoplasm and across the intestinal epithelial cell membrane (Azimi *et al.*, 2020). Bacterial effectors then rebuild the actin cytoskeleton of the host cell, causing the epithelial cell membrane to ripple or stretch outward in order to swallow the bacteria (McGhie *et al.*, 2009). The membrane ruffle's morphology is similar to the phagocytosis process (Patel and Harrison, 2008).

Given that these strains of *Salmonella* are not virulent, their capacity to endure in host cells is essential for disease. After entering a host cell, *Salmonella* is contained within a membrane-bound space called a vacuole that is composed of the host cell's membrane (Azimi *et al.*, 2020). Normally, when foreign substances made of bacteria are present, the host cell's defense system is triggered, which leads to lysosomal fusion and the release of digestive enzymes that break down intracellular bacteria (Chaplin, 2010). However, *Salmonella* uses the type III secretion system to introduce more effector proteins into the vacuole, changing the compartment's structure (Ramos-Morales, 2012). Remodeled vacuoles prevent lysosome fusion, enabling bacterial intracellular survival and multiplication inside the host cell (Fang and Méresse, 2021). The reticuloendothelial system (RES) allows bacteria to be transferred since they can survive inside macrophages (Ellis *et al.*, 2019).

#### **Reservoir**

*Salmonella* is a facultative intracellular bacterium that inhabits macrophage phagolysosomes and is immune to the bactericidal characteristics of antibodies (Singh *et al.*, 2017). Compared to other family members, *Salmonella* is more resilient to various environmental conditions. These bacteria multiply in the pH range of 4–8, at 8°C–45°C, and at water activity higher than 0.94 (Kynčl *et al.*, 2021). Additionally, these bacteria may proliferate in conditions with little to no oxygen (Harrell *et al.*, 2021).

One of the boundaries of human knowledge and practice on farms, food processing facilities, and slaughterhouses is environmental and personal cleanliness. Conversely, food contamination is strongly correlated with the food handler's state of health (Nkhebenyane and Lues, 2020). Foodborne illnesses are a public health concern in both industrialized and developed nations. In the food supply chain, contamination can happen at any point, including in the manufacturing, processing, distribution, and preparation stages (Chebolu-Subramaniana and Gaukler, 2015). There must be strict regulations governing personnel cleanliness on farms and in food processing enterprises.

There are difficulties associated with international trade, including its introduction through travelling abroad and the trading of food, livestock, and animal feed. Contaminated water and inanimate things are potential sources of *Salmonella* (Mukherjee *et al.*, 2019). The increasing AMR to *Salmonella* in recent years as a result of the extensive use of antimicrobial medications in the human and animal sectors adds another layer of uncertainty to the environment around food processing (Nair *et al.*, 2018).

#### **Clinical manifestations**

*Salmonella* strains can be classified as typhoidal *Salmonella* or non-typhoidal *Salmonella* (NTS) based on the clinical presentation of human salmonellosis. In human infections, the four distinct clinical manifestations are gastroenteritis, enteric fever, chronic carrier state, bacteremia, and other extraintestinal complications.

#### **Gastroenteritis**

There exist at least 150 serotypes of *Salmonella* that can cause salmonellosis or nontyphoidal enterocolitis, with the most prevalent serotypes being *S. Typhimurium* and *S. enterica* (Falay *et al.*, 2023). Transmission is usually caused by eating or drinking water tainted with animal excrement rather than human excrement (Teklemariam *et al.*, 2023). Due to the introduction of MDR *S. Typhimurium* DT104, which has been connected to outbreaks linked to beef contamination, hospitalization rates for foodborne salmonellosis have increased (Parker *et al.*, 2021).

Children with systemic salmonellosis are treated with ceftriaxone, whereas those with severe gastroenteritis are frequently given ciprofloxacin (Bruzese *et al.*, 2018). Treatment is typically contraindicated in producing animals, such as pigs, chickens, and cattle, but if necessary, injections can be used together with a variety of other therapies, depending on factors like discontinuation duration (Ghimpețeanu *et al.*, 2022). Since antibiotics might extend the presence of germs in the faeces, they are generally not advised, with the exception of rare circumstances.

#### **Enteric fever**

*Salmonella typhi* is the cause of typhoid fever, whereas *Salmonella paratyphi* A, B, and C are the cause of paratyphoid fever, which has less severe symptoms and a lower fatality rate (Xie *et al.*, 2022). Only humans are pathogenic for both serotypes. Consumption of food or water tainted with human faeces is the usual cause of infection (Crump, 2019). Antibiotic-resistant strains have been discovered in the majority of endemic areas recently, particularly in Southeast Asia, Pakistan, India, and the Middle East (Mina *et al.*, 2023).

About 10% of patients have a chance of dying, relapsing, or suffering from severe side effects like intestinal perforation, gastrointestinal bleeding, or typhoid encephalopathy (Parry *et al.*, 2014). The most frequent occurrence that can be brought on by lingering microbes in the RES is recurrence (Hsiao *et al.*, 2016). There is

a high death rate linked to typhoid encephalopathy, which is frequently accompanied by shock (Leung *et al.*, 2012). Blood transfusions are not necessary for the treatment of mild gastrointestinal bleeding, although if significant blood arteries are implicated, 1%–2% of cases may result in death. Symptoms of an intestinal perforation in sick individuals may include low blood pressure, an elevated heart rate, and stomach pain. Therefore, 1%–3% of hospitalized patients have a very dangerous disease (Aamer *et al.*, 2021).

#### **Chronic carrier state**

Chronic carriers have the ability to spread salmonellosis, which can infect a large number of people, particularly those in the food business (Foster *et al.*, 2021). Not all of the causes of the chronic carrier condition have been identified. *Salmonella* of the nontyphoidal serotype often lives in the digestive system for 6 weeks to 3 months, depending on the serotype (Kurtz *et al.*, 2017). Stool samples from nontyphoidal *Salmonella* patients only contain 0.1% of cases for longer than a year. A chronic carrier status is the outcome of 2%–5% of untreated typhoid infections. In both treated and untreated cases of typhoid, up to 10% will excrete *Salmonella typhi* for 1–3 months, and between 1%–4% will develop into chronic carriers who continue to excrete the bacteria for over a year (Gunn *et al.*, 2014).

#### **Bacteremia and other extraintestinal complications**

Bacteremia is caused by untreated salmonellosis in about 8% of cases (Jakubowski *et al.*, 2018). A dangerous disorder called bacteremia occurs when germs pass through the intestinal barrier and into the circulation (Christaki and Giamarellos-Bourboulis, 2014). It has been linked to extremely invasive serotypes like Dublin or Choleraesuis (Angelo *et al.*, 2016). If there is no apparent cause for a fever, one should consider the possibility of *Salmonella*-induced bacteremia. Antibiotics should be administered to patients who have bacteremia and other problems (Lee *et al.*, 2017).

#### **Diagnosis**

The detection of aseptically collected *Salmonella* in necropsies, environmental samples, feedstuffs, rectal swabs, and food products serves as the basis for diagnosis (Kasturi and Drgon, 2017; Zeng *et al.*, 2021). It can also be identified serologically in animals that have been or are presently infected with certain serovars (Holschbach and Peek, 2018). It is crucial to cultivate vaginal swabs, placentas, fetal entrails, and embryonated egg cells if the reproductive organs are infected, infertility develops, or conception happens (Adem *et al.*, 2022). Numerous methods can be used to identify microorganisms, such as selective agar media to distinguish *Salmonella* from other enterobacteria, pre-enrichment to sensitize badly wounded *Salmonella*, and enrichment media with inhibitory chemicals to inhibit competing organisms (Park *et al.*, 2012). Reliable verification of isolated strains can be achieved by using a range of biochemical, serological,

and molecular studies on pure cultures. The antigenic formula in the Kaufman White scheme can be used to determine the serovars of these microorganisms (Ryan *et al.*, 2017). The antigens called somatic (O), flagellar (H), and virulence (Vi) can be recognized using special typing serum (Wang *et al.*, 2020). Sending isolates to a reference laboratory can be necessary for many laboratories in order to confirm full serologic identity, phage type, and strain genotyping.

#### **Epidemiology**

Typhoid or enteric fever cases are steady at low levels in affluent nations, whereas nontyphoidal salmonellosis cases are rising globally. In developing nations, typhoid fever typically results in the death of 5%–30% of those affected (Antillón *et al.*, 2017). The World Health Organization (WHO) calculates that there are between 16 and 17 million typhoid cases worldwide each year, with 600,000 deaths as a result (World Health Organization, 2018). Although the death rate varies by region, it can still be as high as 5%–7% even with optimal usage of antibiotics (Kalra *et al.*, 2003). However, non-typhoid cases totaled 1.3 billion, resulting in 3 million fatalities (Ao *et al.*, 2015). Between 2 million and 4 million cases of *Salmonella* gastroenteritis and 500 fatalities are reported annually in the United States (Nadi *et al.*, 2020). Since sporadic cases are infrequently recorded and big outbreaks are typically the focus of investigation, it is challenging to calculate more precise salmonellosis numbers. Only 1%–10% of cases of salmonellosis are reported in numerous African, Asian, and South and Central American nations (Teklemariam *et al.*, 2023).

The disease typhoid fever is endemic in many Eastern and Southern European countries, the Middle East, Africa, Central America, Asia, and South America (Hancuh *et al.*, 2023). Typhoid is the most frequent disease among returning tourists in the US and Europe (Muresu *et al.*, 2020). Typhoid fever is most common in endemic areas when it first appears in school-age children and young adults, declines in middle age, and is usually quite low in the first few years of life (Pitzer *et al.*, 2019). The majority of childhood illnesses, particularly in Vietnam's Mekong Delta region, are identifiable despite frequently being mild (Holt *et al.*, 2011). Typhus Mary was the most well-known outbreak of enteric disease. Between 1900 and 1907, at least 22 persons in New York City contracted typhoid fever from hired domestic cook Mary Mallon, which resulted in three fatalities. After being arrested by public health officials in 1907, she was isolated for 3 years. She was released in 1915 with the stipulation to never work as a cook again, but she disregarded that vow and went on to infect at least 25 more people with typhoid disease in a Manhattan maternity hospital. Ultimately, she lived a solitary life until his passing in 1938 (Marineli *et al.*, 2013).

The pathogen's level of contagiousness is determined by the serovar, growth environment, host susceptibility, and bacterial strain of *Salmonella*. Conversely, host

variables that regulate vulnerability to infection comprise age, underlying illness, and immunological weakness or digestive tract health (Schultz *et al.*, 2018). *Salmonella* can spread to infectious doses of  $10^3$ – $10^9$  CFU/g (Andino and Hanning, 2015). The young, old, pregnant, and immunosuppressed (YOPI) categories are particularly vulnerable to infection from salmonellosis, with outbreaks stemming from a single food source showing that as little as 1–10 cells can cause the disease (Dietrich *et al.*, 2023).

#### **Transmission**

*Salmonella* can be found in water for several days to several months, but it is also common and extremely persistent in dry settings (Wibisono *et al.*, 2020). *Salmonella enterica* serovars can infect humans and animals and have a variety of hosts and reservoirs (Silva *et al.*, 2014). Most *Salmonella enterica* serovars are host-adapted, which means they can infect and cause sickness in a wide range of hosts, with the exception of a small number of host-restricted serovars (Andino and Hanning, 2015). Animals that are asymptomatic but are considered “carriers” of *Salmonella* can develop clinical illness or subclinical infections (Usmael *et al.*, 2022). For instance, prior research has demonstrated that subclinical infections in hens can last longer than 22 weeks (Ruvalcaba-Gómez *et al.*, 2022). In other research indicates that carrier pigs are a significant source of contamination for the farm’s other animals, the environment, and harvest-stage carcasses (Soliani *et al.*, 2023). These carriers are crucial to the ongoing spread of *Salmonella* in the environment and on farms because they can periodically and continually excrete the bacterium in their faeces without exhibiting any symptoms (Ehuwa *et al.*, 2021). Similar to this, it has been demonstrated that pets like dogs and cats carry these germs around asymptotically. As a result, when they periodically excrete these bacteria through their faeces, they can contaminate the environment and other animals that produce food (Drózdź *et al.*, 2021). Transmission via vertical and horizontal paths are two other significant types. Vertical transmission is when germs are passed from parents to children (Liu *et al.*, 2022). Since Enteritidis serovars have a particular affinity for the reproductive system of hens, vertical transmission is particularly relevant when it comes to *Salmonella* infections in poultry (Shaji *et al.*, 2023). In this instance, the parent chicken contracts a systemic infection that results in ovarian infection and the formation of eggs in the fallopian tubes, which transmits the infection to the offspring by transovarian infection (Shah *et al.*, 2017). Enteritidis serovars can also migrate from the cloaca to the reproductive organs in order to obtain access to eggs (Jiang *et al.*, 2023). There is growing evidence that in dairy cows, *Salmonella* can also be vertically passed from mother to foetus during gestation (Hanson *et al.*, 2016). Conversely, horizontal transmission happens via the aerogenous or feco-oral pathway (Gast *et al.*, 2020). Salmonellosis can also

be introduced into livestock through recently acquired and infected birds (Shaji *et al.*, 2023). The disease can also spread on farms through foreign objects, tainted drinking water, unclean feed and feeders, asymptomatic carriers, and animal excrement from clinically infected animals (Mkangara, 2023).

The spread of *Salmonella* from one building or livestock facility to another, as well as the survival of livestock buildings and facilities, are significantly aided by pests including cockroaches, flies, and rodents (Djeffal *et al.*, 2018). *Salmonella* can be carried in the intestinal tract of rodents without any signs or clinical disease, making them significant reservoirs and vectors of the bacteria (Deng *et al.*, 2007). This bacterium can be acquired from the excrement of sick or wild animals on farms, and it is frequently linked to contamination of feed, water, and grain kept on farms (Wibisono *et al.*, 2020). Flying insects serve as mechanical carriers that facilitate the spread of bacteria from one farm to another and from animals to people (Bertelloni *et al.*, 2023). Animals raised on farms contract the disease by eating *Salmonella*-contaminated flies. Flies near chicken farms and in the surrounding environment have been found to harbour *Salmonella* (Holt *et al.*, 2007). *Salmonella* infections are thought to be mostly spread by wild animals, including wild birds and other wildlife (Hoelzer *et al.*, 2011). They are in charge of introducing and dispersing germs into animals through contaminated feed, water, or the surrounding environment. It has been demonstrated that human trafficking on farms raises the possibility of *Salmonella* infections in hens, chickens, and pigs (Teklemariam *et al.*, 2023). A different study found a direct link between the number of tourists and the incidence of *Salmonella* on farms (Rodríguez-Hernández *et al.*, 2021). The results of this investigation indicated that a rise in farm visitor numbers was linked to an increased incidence of *Salmonella*.

#### **Risk factor**

Risk factors for *Salmonella* infections include a variety of foods, for example contaminated chicken, beef and pork (Ehuwa *et al.*, 2021). Additionally, *Salmonella* can be found in a variety of crops and sprouts (Cui *et al.*, 2017). This bacterium may also be present in a number of processed foods, including pot pie and chicken nuggets (Mkangara, 2023). Eating food that has been obtained from locations other than supermarkets increases the risk of salmonellosis (Ehuwa *et al.*, 2021). Other recognized risk factors include eating ice cream, flavoured iced drinks, consuming food from street vendors, coming into contact with patients or disease carriers, and raw fruit and vegetables that are cultivated in fields that have been fertilized with manure (Batool *et al.*, 2022). *Salmonella* infection will be spread by unhygienic labour practices when handling and preparing food as well as poor waste disposal (Mkangara, 2023). The different management strategies employed, the degree of stocking, whether

the animals are housed or not, and the epidemiological traits of *Salmonella* all affect the clinical manifestations of the disease in large animals (He et al., 2023).

The animal's reaction to a *Salmonella* infection is determined by the size of the challenge dose and its immune status, which is based on its prior infections, exposure to stressors, particularly in older animals, and its colostrum consumption in newborns (Higginson et al., 2016). It is acknowledged that intensifying livestock production across all species has a major risk of raising the incidence of novel illnesses (Sargeant et al., 2021). Any significant change in the way a herd or group of animals is managed can lead to the clinical manifestation of an illness if it is already present in the animals (Cummings et al., 2009). *Salmonella* is sensitive to dryness and sunshine; thus, temperature and humidity are crucial (Bashir et al., 2022).

#### **Antibiotic resistance**

*Salmonella* strains developing antibiotic resistance is a major global health concern. *Salmonella* resistance to a particular antibiotic, specifically chloramphenicol, was first documented in the early 1960s (Aslam et al., 2018). Since then, many nations, including the UK, the US, and Saudi Arabia, have seen a rise in the frequency of isolating *Salmonella* strains that are resistant to one or more antimicrobial treatments (Montone et al., 2023). Traditional first-line therapies for *Salmonella* infections involve the use of antibiotics including chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole (Veeraraghavan et al., 2021).

A multidrug resistant (MDR) strain of *Salmonella* is resistant to at least 3 different classes of antibiotics. MDR phenotypic features have become more common over time in *S. typhi* at higher levels and *S. paratyphi* at lower levels. Two continents where the MDR phenotype of *S. typhi* isolates is prevalent are Africa and Asia (Eng et al., 2015). In a surveillance survey spanning five Asian nations, MDR isolates of *S. typhi* were found at higher concentrations in India, Pakistan, and Vietnam than in Indonesia and China (Ochiai et al., 2008). Similar information is shown in other published reports, which show that MDR *S. typhi* is more common in Pakistan, India, Nepal, and Vietnam than it is in China, Indonesia, and Laos (Effa et al., 2011).

Fluoroquinolones and broad-spectrum cephalosporins are now the recommended antimicrobial medicines for the treatment of MDR *S. typhi* due to the development of resistance to traditional antibiotics (Veeraraghavan et al., 2018). However, research suggests that cases of typhoidal *Salmonella* are becoming increasingly resistant to fluoroquinolones (Piekarska et al., 2023). *S. paratyphi* exhibits more fluoroquinolone resistance than *S. typhi* in nations with a higher prevalence of MDR isolates (Kumar et al., 2017). Isolates from Pakistan, India, and Vietnam exhibited significant incidence rates of 59%, 57%, and 44%, respectively, of nalidixic acid resistance, which is utilized as a marker

of decreased sensitivity to ciprofloxacin and other fluoroquinolones (Eng et al., 2015).

Regarding NTS, since the 1990 release of the MDR strain *S. Typhimurium* DT104, the number of strains exhibiting the MDR phenotype has grown in numerous nations (Boyd et al., 2002). According to statistics from the National Antimicrobial Resistance Monitoring System (NARMS) for the years 2005–2006, 4.1% of clinical isolates in the US demonstrated decreased sensitivity to cephalosporins, and 84% of NTS isolates exhibited the MDR phenotype (Rincón-Gamboa et al., 2021). More thorough data (1996–2007) is provided by NARMS, which also reports the rise of NTS isolates resistant to ceftriaxone and nalidixic acid (Crump et al., 2011). Public health officials are concerned about this phenomenon in terms of clinical care and infection prevention. Data from a surveillance study of 135,000 NTS clinical isolates done in Europe between 2000 and 2004 revealed that 20% of isolates were nalidixic acid resistant and 15% of isolates had the MDR phenotype (Meakins et al., 2008).

#### **Public health importance**

Globalization, technological advancements in travel, and the expansion of international trade between numerous nations have recently resulted in the rapid spread of foodborne pathogens, contaminants in food, and other infections that may be dangerous to human health (Bintsis et al., 2017). Since surveillance systems are crucial economically, there is a growing awareness of the necessity to implement them in order to guarantee food safety and pinpoint the items that are linked to foodborne disease outbreaks. Furthermore, finding a single tainted food item might lead to the wastage of tons of food, which can impair international trade and cause financial losses for the producing industry (Ishangulyyev et al., 2019). One of the most often reported foodborne disease outbreaks globally is salmonellosis, which is typically prevalent in impoverished nations like Africa, India, and Asia (Popa and Papa, 2021). Due to its high endemicity, the challenge of putting control measures in place, and its notable rates of morbidity and mortality, this illness poses a hazard to public health (Galán-Relaño et al., 2023). *Salmonella* has been connected to outbreaks and isolated cases of foodborne illness in humans all across the world, making it one of the organisms with the biggest effects on human populations, according to the World Health Organization (WHO, 2018). Since outbreaks of salmonellosis have been linked to chicken and poultry products, including eggs, poultry is widely acknowledged as a primary source of the disease (Andino and Hanning, 2015). Humans typically contract the disease by eating food tainted with animal faeces or by cross-contaminating food with other substances (Teklemariam et al., 2023).

Typhoid strains *S. typhi* and *S. paratyphi* are the cause of enteric fever, which is prevalent in Southeast and Central Asia and is estimated to cause 200,000 fatalities and 22 million illnesses annually (Crump and



Mintz, 2010). NTS serovars are common and typically linked to particular species. This bacterium typically causes self-limiting gastroenteritis in humans, which manifests as fever, vomiting, diarrhea, and cramping in the stomach (Fleckenstein et al., 2021). Prolonged faecal bacterial shedding lasting longer than a month may accompany these symptoms. The most prevalent type of NTS infection, gastroenteritis, is thought to cause 93.8 million cases and 155,000 fatalities worldwide each year (Peter et al., 2023). According to monitoring data from 2001 to 2005, *S. enterica* (12%) is the most commonly isolated serovar that causes NTS infections globally, followed by *S. Typhimurium* (4%) from clinical isolates that have been recovered (Kumar et al., 2022). Similar to this, *S. enterica* has been found to be the most prevalent serotype in Latin America, Asia, and Europe, where it accounts for 31%, 38%, and 87% of clinical isolates, respectively (Eng et al., 2015). Conversely, common serotypes of *S. enterica* and *S. Typhimurium* were found to be prevalent in 26% and 25% of recovered clinical isolates in Africa, respectively (Andoh et al., 2017). Salmonellosis was expected to cost US\$ 2.71 billion a year for 1.4 million patients in 2010 (Andino and Hanning, 2015). Similar estimates place the annual cost of medical expenses, lost productivity, and sick leave related to a high frequency of salmonellosis in the US between US\$ 1.3 and US\$ 4.0 billion (Whiley and Ross, 2015).

#### **Economic impact**

The prevalent intestinal illness known as salmonellosis, which is mostly caused by tainted meat and poultry, is thought to cost nations billions of dollars annually and divert resources from development (Popa and Papa, 2021). Salmonellosis is one of the causes of significant economic losses in livestock due to clinical disease costs which include death, diagnosis and treatment of clinical cases, laboratory diagnosis costs, cleaning and disinfection costs, as well as control and prevention costs (Abdulhaleem et al., 2019). Farmers lose out on feed efficiency, decreased weight increase, and deaths from salmonellosis (Evangelopoulou et al., 2015). Human foodborne salmonellosis is a serious health issue in many nations. Furthermore, treating salmonellosis can be expensive. Financial expenses can have an impact on the entire production chain in addition to being associated with the diagnosis, treatment, and prevention of human diseases (Niemi et al., 2019). Even in affluent nations, animal products pose the greatest food risk associated with chicken meat, as seen by the high prevalence of salmonellosis in many developing nations, such as Zimbabwe, Brazil, India, and Egypt (El-Aziz, 2013). *Salmonella enterica* is spread by seemingly healthy chicken eggs into human meals (Foley et al., 2013). Animal products can become contaminated with *Salmonella* at several points in the food chain, such as during manufacturing, processing, distribution, retail marketing, handling, and preparation (Mkangara, 2023).

#### **Treatment**

Antibiotic resistance is spreading over the globe, thus choosing medications needs to be done carefully. Typically, salmonellosis resolves on its own and does not need special care. In cases of severe diarrhea, intravenous fluids may be necessary for rehydration (Andrews et al., 2017). Antibiotic therapy is required for systemic infections in animals and humans with septicaemia and should be based on the antimicrobial susceptibility of the isolate that is cultured (Rojas-Sánchez et al., 2023). Antibiotics are not advised for simple cases and should only be used if the infection has spread or is likely to spread from the gut to the bloodstream and other organs (Zha et al., 2019). Typically, aminoglycosides, trimethoprim-sulfamethoxazole, fluoroquinolones, and chloramphenicol have proven to be very active against *Salmonella* (Nair et al., 2018). The majority of the time, this bacterium is resistant to cefapirin, ampicillin, clindamycin, and erythromycin (Adzitey, 2018). The two antibiotics to which high bacterial resistance frequency was shown were tetracycline and streptomycin (Pezzella et al., 2004). Extra supportive care, such as the use of colloid, may be necessary when salmonellosis is accompanied by a severe clinical illness (Worley, 2023).

#### **Control**

Salmonellosis can be prevented and controlled by implementing the HACCP principle (Ehuwa et al., 2021). Biosafety and biosecurity need to be included into farm management procedures (Butucel et al., 2022). These actions are crucial for controlling infections. Requirements for entering the livestock industry include excellent health and procurement from reliable vendors with inspected breeding and hatching facilities (Fanissa et al., 2022). On farms, *Salmonella* can also spread by means of workers, vehicles, water, food, rubbish, clothing, shoes, rats, wild birds, pets, tools, and a host of other things (Ehuwa et al., 2021). Restricting the number of individuals who visit the farm, using protective gear, and donning cleaned boots are all ways to stop *Salmonella* from getting inside (Course et al., 2021). Additionally, employees need to understand the fundamentals of hygiene, such as cleaning their hands and feet. Regular cleaning and disinfection must be planned into the administration of the entire farm (Trampel et al., 2014). It is necessary to collect samples from the surroundings, drinking water, feeding places, walls, and floors to assess the effectiveness of disinfection on farms (Gržinić et al., 2023).

Antibiotic use can result in resistance issues and implementing hygienic measures to prevent salmonellosis is challenging. A multi-step strategy is needed to lower the occurrence of *Salmonella* at every stage of cultivation, hatching, raising, transportation, and processing (Obe et al., 2023). Salmonellosis can be decreased with the use of a live-attenuated recombinant DNA vaccine in conjunction with a thorough control program for animals, feed, and animal products (Sears et al., 2021). The growth of microorganisms in meat

and poultry products can be controlled by keeping the cold chain at or below 10°C, especially when it comes to *Salmonella* during storage and transit (Cardoso *et al.*, 2021). Complete immunity to illness is not guaranteed by vaccination. Preventing the vertical transmission of *S. enterica* between bird generations is an efficient method of managing *Salmonella* in eggs (Liu *et al.*, 2022). The idea is a top-down strategy that involves testing and eradicating *Salmonella* starting at the top of the production pyramid and working its way down (Sivaramalingam *et al.*, 2013).

### Conclusion

*Salmonella* infections (Salmonellosis) continue to be one of the most common foodborne illnesses with significant global public health impact. Worldwide, there is an estimated 93.8 million cases and about 155,00 fatalities. Primarily, food-producing animals such as poultry and poultry products, swine, and cattle have been identified as important sources of salmonellosis. Additionally, raw fruits and vegetables are among other food types that have been linked to the spread of *Salmonella* spp. Antibiotic abuse/misuse can result in the development, emergence, or evolution of MDR strains. The epidemiological situation of salmonellosis, especially due to MDR bacterial pathogens has further exacerbated its treatment challenges as the emergence of MDR *Salmonella* strains complicates and limits treatment options. Implementing hygienic measures to prevent salmonellosis due to these MDR strains is challenging; thus, it is therefore imperative for physicians and veterinarians to carefully choose antibiotics for use to curtail the emergence of MDR strains. Additionally, the continued increasing incidence, emergence, and spread of MDR *Salmonella* strains has resulted in significant economic consequences for people, the food sector, and thus, needs urgent attention and intervention.

### Acknowledgments

The authors thank the Universitas Airlangga.

#### Authors' contributions

SRA, ARK, and WPL drafted the manuscript. TRF, IBM, and MD revise and edits the manuscripts. ML, SHW, MAA, and SA took part in preparing and critical checking this manuscript. IPH, AH, and OSMS edits the references. All authors read and approved the final manuscript.

#### Conflict of interest

The authors declare that there is no conflict of interest.

#### Funding

This study was supported in part with the Program Penelitian Riset, Teknologi, dan Pengabdian Kepada Masyarakat, in the fiscal year 2023, with grant number: 0536/E5/PG.02.00/2023.

#### Data availability

All references are open access, so data can be obtained from the online web.

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