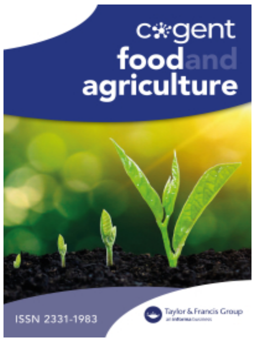

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Prevalence of antibiotic and heat resistant *Salmonella* species in the dairy value chain: a review

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ABSTRACT

Milk and dairy products are essential constituents of balanced and nutritious diets worldwide; however, they are susceptible to contamination by *Salmonella* species, which can cause salmonellosis in consumers. This contamination raises significant public health concerns as epidemiological evidence has repeatedly identified milk and dairy products as sources of infectious disease outbreaks. Additionally, *Salmonella* infections can also affect dairy animals, impacting milk quality and resulting in economic losses for farmers. Traditional control methods include the use of antibiotics and heat, but *Salmonella* can develop resistance to these interventions, complicating efforts to ensure safety in the dairy industry. This review highlights the global prevalence of *Salmonella* in the dairy value chain, factors contributing to its contamination, and the demographics most affected. It also highlights commonly reported serotypes, their resistance mechanisms, and the urgent need for implementation of control strategies to reduce the public health burden of *Salmonella* contamination in milk and dairy products, with particular emphasis on resource-limited settings.

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1. Background

The dairy sector plays a significant role in communities in many nations throughout the world (Virto et al., 2022). Global demand for milk has remained consistently high, driving a substantial increase in production, with more than 77% growth recorded over the past three decades (Virto et al., 2022). Between 1992 and 2022, global milk production increased markedly from 524 million to 930 million tonnes (Virto et al., 2022). India constitutes the greatest share of global production with 22%, followed by the United States, Pakistan, China, and Brazil (Salter, 2017). The rise in milk production is chiefly attributable to the escalating global demand for milk and dairy products (Virto et al., 2022). Compared to the trend around the world, the growth of the sector in Africa is generally slow (Virto et al., 2022). This is because of the high levels of poverty especially in sub-Saharan African countries, climate change, pests and diseases which do not favor diary production (Ndambi et al., 2014).

Milk and dairy products serve a pivotal function in maintaining a balanced and nutritious diet, offering key nutrients such as calcium, protein, and vitamins that are essential for maintaining health across all age groups (Salter, 2017). Calcium (which makes up 49% of the world's nutrient availability), vitamin B2 (24%), lysine (18%), and dietary fat (15%) are all primarily found in milk. Additionally, it supplies almost 10% of the world's nutrient availability for protein, vitamins A, B5, and B12, and the nine essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) (Ndambi et al., 2014; Salter, 2017). These nutrients are vital for the development and maintenance of strong bones as well as other body tissues (Ortuzar et al., 2018). The nutritional composition of milk and dairy products, in addition to their almost neutral pH and high water activity (aw), also provides a highly conducive milieu for the proliferation of a number of bacteria, including *Salmonella*

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(Ortuzar et al., 2018; Reta et al., 2016). *Salmonella* contaminates non-pasteurized milk and dairy products including cheese, ice cream, butter, and powdered milk at various stages of the dairy value chain (Cummings et al., 2010; Eng et al., 2015; Thornton, 2010). The stages involved in delivering milk and dairy products to the final consumer include; production, transportation, processing, packaging, and storage (Thornton, 2010). Dry cleaning methods should be used to maintain dryness in processing areas to minimize milk contamination, while water usage should be restricted to prevent the dissemination of contaminants through moisture (Thornton, 2010). The prevalence of *Salmonella* in milk and dairy products is attributed to a number of determinants. These determinants encompass; poor milking hygiene, poor sanitary conditions during milk processing, transportation and storage (Ortuzar et al., 2018; Reta et al., 2016). An outbreak of salmonellosis, a disease that can be fatal, particularly in children and immunocompromized individuals, can result from the contamination of milk and dairy products with *Salmonella* (Nicolas et al., 2006). Antibiotics and heat are applied globally to control animal and human pathogens including *Salmonella* (Virto et al., 2022). However, antibiotic and heat-resistance of species of *Salmonella* isolated from dairy products and milk has been reported in various countries (Owusu-Kwarteng et al., 2020). Such countries include; Uganda (Wolff et al., 2017), Kenya (Nyokabi et al., 2021), Rwanda (Kamana et al., 2017), Ethiopia (Gebeyehu et al., 2022), Ghana (Parry-Hanson Kunadu et al., 2018) and India (Singh et al., 2018). Therefore, this review aims at documenting current knowledge on prevalence of antibiotic and heat-resistant *Salmonella* spp. in the dairy value chain. Understanding the extent of the public health burden posed by *Salmonella* contamination in dairy products is fundamental to improving milk safety and effectively managing *Salmonella* outbreaks.

Salmonella can contaminate milk and dairy products at various stages of the dairy value chain. The stages of the dairy value chain include: production, transportation, collection at milk collection centers, processing, retailing, and consumption (Figure 1).

2. Growth conditions of *Salmonella*

Salmonella requires various conditions to proliferate. The ideal temperature range for *Salmonella* growth is between 8 °C and 45 °C and the optimum pH ranges from 4 to 9 at water activity values above 0.94

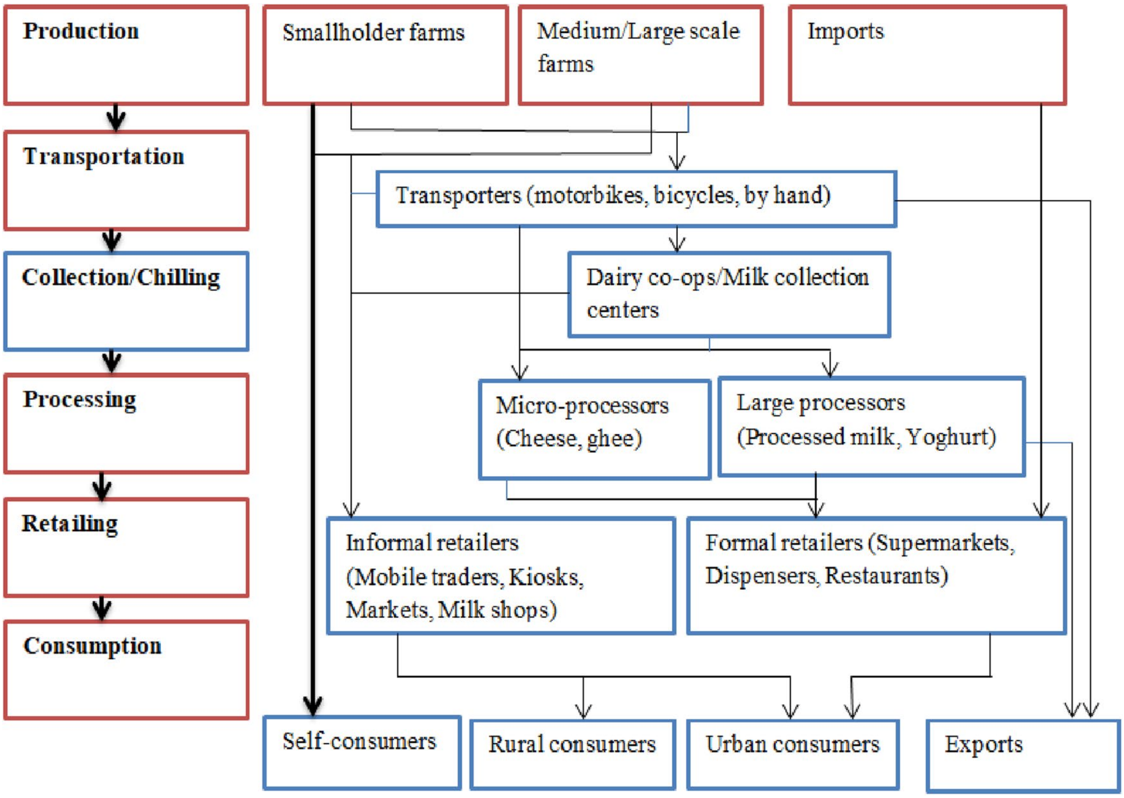

Figure 1. Overview of the various stages within the dairy value chain (Kamana et al., 2017).

(Tindall et al., 2005). Owing to their thermosensitive properties, most *Salmonella* species are effectively inactivated at conventional cooking temperatures (>70 °C). Nonetheless, variations in serotype and the compositional characteristics of the food matrix may influence the resistance to thermal inactivation of the organism, necessitating adjustments in cooking and cooling parameters to ensure complete inactivation (Tindall et al., 2005). For instance, between −23 °C to −18 °C, some *Salmonella* species can survive for over 7 years (Trabelsi et al., 2010). *Salmonella* Enteritidis can survive at high temperatures of 80 °C in lower moisture dairy products with reduced water activity such as butter and dehydrated milk powders (Yang et al., 2020). *Salmonella*-contaminated milk powder kept at varying temperatures did not significantly lower the number of viable *Salmonella* cells after 15 weeks (Yang et al., 2020). Viable *Salmonella* cells were found after 10 hours at 76.6 °C, demonstrating the bacteria's remarkable heat resistance in dehydrated milk powder (Yang et al., 2020). Therefore, the difficulty in controlling *Salmonella* species in the dairy value chain could be attributed to their capability to withstand adverse conditions including very high or low temperatures, pH, and humidity (Trabelsi et al., 2010). For example, heat-sensitive molecules like proteins, DNA, and RNA typically stop functioning when bacterial cells are thermally inactivated (Mañas & Pagán, 2005). The molecules play structural and physiological roles in the bacterial cell. However, loss of water from bacterial cells at low water activity of low-moisture dairy products may sometimes produce protein structures that are more stable to prevent denaturation by heat (Mañas & Pagán, 2005). This could account for *Salmonella*'s ability to survive at high temperatures, particularly in foods with minimal moisture content.

3. *Salmonella* species and their classification

Salmonella is a genus within the Enterobacteriaceae family, comprising facultatively anaerobic, rod-shaped, Gram-negative bacteria that usually inhabit the intestines of humans and other warm-blooded animals (Coorevits et al., 2008; Rozwandowicz et al., 2018; von Wintersdorff et al., 2016). The genus *Salmonella* comprises of potentially pathogenic species of bacteria which are responsible for a broad spectrum of infections that lead to human and animal morbidity and mortality (Sommer & Bäckhed, 2013). *Salmonella enterica* and *Salmonella bongori* are two typical pathogenic species of the genus *Salmonella* (Gebeyehu et al., 2022). While *S. enterica* can infect a number of warm-blooded animals, *Salmonella bongori* is only found in cold-blooded animals (Gebeyehu et al., 2022). *Salmonella enterica* subsp. enterica (I), enterica subsp. salamae (II), enterica subsp. arizonae (IIIa), enterica subsp. diarizonae (IIIb), enterica subsp. houtenae (IV), and enterica subsp. indica (VI) are the six subspecies of *Salmonella enterica* that have been identified. More than 2700 distinct *Salmonella* serotypes have been classified according to variations in the somatic 'O' and flagellar 'H' antigens present on the bacterial outer membrane (Gebeyehu et al., 2022). Almost 1500 of these are *Salmonella enterica* subsp. enterica (Gebeyehu et al., 2022). Among the diverse *Salmonella* species, *Salmonella enterica* subsp. *enterica* is the most prevalent pathogenic and zoonotic subspecies, resulting in a broad spectrum of salmonellosis cases in both humans and animals (Sommer & Bäckhed, 2013). There are different serotypes of *S. enterica* subsp. enterica distinguished based on their genetic diversity and biochemical characteristics (Zakrzewski et al., 2022). The most common ones include *S.* Abortusovis, *S.* Enteritidis, *S.* Infantis, *S.* Miami, *S.* Montevideo, *S.* Muenchen, *S.* Muenster, *S.* Paratyphi A, B and C, *S.* Poona, *S.* Sendai, *S.* Typhi, *S.* Thompson, *S.* Typhimurium, *S.* Anatum, *S.* Seftenberg, *S.* Newington, *S.* Oranienburg, and *S.* Habana (Zakrzewski et al., 2022). However, *Salmonella enterica* subsp. *enterica* serotype Typhimurium and *Salmonella enterica* subsp. *enterica* serotype Typhi rank among the most virulent (Asefa et al., 2023; Cummings et al., 2010; Eng et al., 2015). The genetic divergence between the two serotypes accounts for distinct differences in their pathogenicity, influencing both the nature and severity of the infections they cause (Sobeih et al., 2020). Based on their clinical characteristics, *Salmonella* serotypes are categorized into typhoidal and non-typhoidal *Salmonella* (NTS) (Smith et al., 2016). Typhoid fever, commonly known as enteric fever, is an aggravating, occasionally fatal illness caused by human-specific strains of *Salmonella enterica* subsp. *enterica* serotypes Typhi, Sendai, and Paratyphi A, B, and C. Typhoid fever clinically manifests as septicemia, acute enteritis, and chronic enteritis, enterocolitis with congestion, hemorrhage, and edema (Rozwandowicz et al., 2018; Sommer & Bäckhed, 2013; Zakrzewski et al., 2022). The remaining serotypes such as *S.* Abortusovis, *S.* Enteritidis, *S.* Infantis, *S.* Miami, *S.* Montevideo, *S.* Muenchen, *S.* Muenster, *S.* Poona, *S.* Thompson, *S.* Anatum,

Table 1. Global prevalence of *Salmonella* serotypes in cattle between 2012 and 2019 (Sommer & Bäckhed, 2013).

Serotypes identified	Prevalence (%)	Study location/period
S. Typhimurium, *S.* Dublin, *S.* Anatum	7.2	India, Dairy farms, 2012–2013
S. Typhimurium, *S.* Newport	10.5	United States, Beef cattle, 2017
S. Typhimurium, *S.* Montevideo	4.8	South Korea, Dairy cattle, 2010–2011
S. Heidelberg, *S.* Typhimurium, *S. Muenchen*	15.0	UK, Cattle slaughterhouses, 2011–2012
S. Typhimurium, *S.* Enteritidis, *S. Dublin*	12.3	Finland, Cattle farms, 2014–2015
S. Agona, *S.* Infantis	3.6	Russia, Dairy cattle, 2018–2019
S. Typhimurium, *S.* Dublin, *S.* Montevideo	8.9	United States, Beef cattle, 2016–2017

Table 2. Global prevalence of *Salmonella* serotypes in goats between 2014 and 2020 (Sommer & Bäckhed, 2013).

Serotypes identified	Prevalence (%)	Study location/period
S. Typhimurium, *S.* Enteritidis, *S.* Derby, *S.* Infantis	1–10	Europe, 2014
S. Typhimurium, *S.* Enteritidis, *S.* Virchow, *S.* Newport	5–12	India, 2013
S. Typhimurium, *S.* Dublin, *S.* Newport	3–8	Africa, 2015
S. Typhimurium, *S.* Infantis, *S.* Anatum	2–7	Middle east, 2012
S. Typhimurium, *S.* Heidelberg, *S.* Muenster	1–4	USA, 2017
S. Typhimurium, *S.* Enteritidis, *S.* Infantis	3–5	Brazil, 2018
S. Typhimurium, *S.* Derby, *S.* Enteritidis	1–6	China, 2020

S. Seftenberg, *S.* Newington, *S.* Oranienburg, and *S.* Habana are NTS and are mainly found in animals as the major reservoirs (von Wintersdorff et al., 2016). *Salmonella* that is non-typhoidal can lead to bacteremia, and gastroenteritis. Diarrhea, high temperature with prostration are also possible symptoms (Sommer & Bäckhed, 2013).

Research indicates that different countries have different prevelance rates of *Salmonella* serotypes in cattle. However, *Salmonella* Typhimurium and *Salmonella* Dublin are the most frequently detected serotypes in cattle worldwide (Table 1).

As shown in Table 2, the distribution of *Salmonella* serotypes among goat populations demonstrates significant regional variation. In Europe, Africa, and Asia, the prevalence rate of *Salmonella* serotypes ranges from 1% to 12%. *Salmonella* Typhimurium is among the most commonly reported serotypes in goats across different regions. *Salmonella* Enteritidis and *Salmonella* Derby have also been frequently reported in various studies. Other serotypes like *S.* Newport, *S.* Virchow, and *S.* Heidelberg have been reported in specific regions. Developed countries generally report lower prevalence in goats (1–5%). Higher prevalence rates of *Salmonella* (5–12%) are commonly reported in developing countries due to inadequate animal husbandry practices and restricted access to quality veterinary care.

4. The global public health burden of *Salmonella*

Worldwide, *Salmonella* species are among the most prevalent pathogenic bacteria, frequently responsible for infections in humans and animals across both industrialized and low- to middle-income countries (Amorim & Nascimento, 2017). Salmonellosis is the disease they cause, and it either presents as mild food poisoning or as acute gastroenteritis, with symptoms like fever, chills, nausea, vomiting, diarrhea, and prostration (Amorim & Nascimento, 2017). The increased mortality and morbidity caused by salmonellosis in animals causes significant economic losses to farmers especially in sub-Saharan Africa (Amorim & Nascimento, 2017). Humans may contract salmonellosis from infected animals through direct or indirect contact with them (Zakrzewski et al., 2022). Contamination of the environment and food milk and dairy products with *Salmonella* species is primarily caused by the feces of infected humans and animals (Zakrzewski et al., 2022). *Salmonella* contamination of food, especially milk and dairy products, is widely recognized as a significant global public health concern with the potential to cause severe and life-threatening illnesses (Zakrzewski et al., 2022).

Foodborne illnesses, which affect 10% of the world's population, cause over 33 million deaths annually and have a serious detrimental effect on public health (von Wintersdorff et al., 2016). *Salmonella* species are the predominant causative agents of foodborne infections, exerting a substantial impact on public health (Wang et al., 2020). *Salmonella* has a significant negative influence on human health worldwide, with 93.8 million infections, of which about 80.3 million cases are food-borne leading to 155,000

Table 3. The incidence of non-typhoidal *Salmonella* in different regions in 2022 (Asefa et al., 2023).

Regions	Incidence (cases per 100,000 population)	Deaths (per 100,000 population)
Europe	10.7	1.5
Latin America	15–26	1.5–2.6
North America	15–20	0.5
Asia	27	2.7
Africa	37.2	4.5

Table 4. The global incidence of non-typhoidal *Salmonella* in the different age groups in 2022 (Asefa et al., 2023).

Age groups	Incidence rate (cases per 100,000 population)	Mortality rate (deaths per 100,000 population)
<5 years	200–400	2–5
5–14 years	50–100	0.5–1.5
15–49 years	20–50	0.5–1
50–64 years	20–40	1–3
>65 years	20–60	3–7

fatalities each year (Zakrzewski et al., 2022). *Salmonella enterica* affect over 17 million people worldwide each year (Diep et al., 2019). Every year, typhoid fever due to *S. enterica* leads to the mortality of 16 million people world-wide (Zakrzewski et al., 2022). In the United States alone, *Salmonella* infections are projected to be responsible for roughly 1.4 million illnesses, over 16,000 hospital admissions, and 580 mortalities annually (Zakrzewski et al., 2022).

Table 3 shows that the greatest prevalence of non-typhoidal *Salmonella* occurs in sub-Saharan Africa and Asia, with reported incidence rates of 37.2 and 27 cases per 100,000 population, respectively. In contrast, Europe reports a lower incidence rate of 10.7 cases per 100,000, accompanied by relatively low mortality. These results indicate that non-typhoidal *Salmonella* infections occur with greater frequency in low- and middle-income countries, primarily driven by factors such as insufficient sanitation, suboptimal food safety measures, and restricted healthcare access.

Table 4 shows that globally, the greatest incidence of non-typhoidal Salmonella infections occurs among children below 5 years, with 200–400 cases per 100,000 population. The incidence declines with age after 5 years to 50–100 cases per 100,000 population. In adults (aged 15–49), the burden is moderate, and the mortality rate is lower (20–50 cases per 100,000 population) compared to younger children or elderly individuals. Individuals aged 65 years and above exhibit the highest mortality rates associated with *Salmonella* infections (3–7 deaths per 100,000 population), primarily due to the greater likelihood of comorbidities such as diabetes and heart disease that compromise immune response and increase susceptibility to severe illness.

5. Contamination of milk and dairy products with *Salmonella* species

Salmonella species are not initially present in milk produced from the mammary glands of healthy animals (Asefa et al., 2023). Therefore, post-harvest handling practices, milking containers and personnel remain as the main sources of *Salmonella* species that contaminate milk and dairy products (Asefa et al., 2023; Singh et al., 2018; Stulova et al., 2010). Additional notable sources of *Salmonella* contamination include soiled udders of animals, unsanitary traditional pre- and post-milking practices, the milking environment, and contaminated water (Kamana et al., 2017). *Salmonella* species represent a significant percentage of spoilage microflorae of milk and dairy products causing bacteremia in infants and adults, especially in poor nations (Stulova et al., 2010). Due to *Salmonella*'s capacity to thrive on dirty milking equipment, contamination from udders, improperly chilled milk, and milking of cows with mastitis, *Salmonella* rates are frequently high in various dairy products (Kamana et al., 2017). Furthermore, pooling of milk from different suppliers without prior testing also results in occurrence of *Salmonella* species in milk (Owusu-Kwarteng et al., 2020). Therefore, animal health, improper storage conditions, and inadequate hygiene standards at the producing farms are the main factors influencing the contamination of milk with *Salmonella* species along the dairy value chain (Singh et al., 2018).

Salmonella species are known as versatile bacteria capable of adapting to a broad spectrum of pH values (4 to 9), water activity levels (aw 0.60 to 0.94), and temperature ranges (6 to 46 °C), extending beyond their optimal growth conditions (Stulova et al., 2010). *Salmonella* species from contaminated raw milk can end up contaminating pasteurized milk and processed dairy products (Stulova et al., 2010). For instance, a study carried out in Ghana reported prevalence of 17.7% for *Salmonella* in raw milk. Whole genome sequencing identified 10 isolates as *Salmonella enterica* serotype Muenster, while 9 strains (5.9% of raw milk samples) were identified as *S*. enterica serotype Legon. Notably, *S*. Legon was isolated from raw milk sold at the Nima milk market, whereas *S*. Muenster was detected in samples obtained from the Tulaku and Ashaiman milk markets in Accra (Babio et al., 2015). *Salmonella* was found to be 6.3% prevalent in cottage cheese from different parts of Ethiopia in samples collected from producers and merchants in Oromia (Stulova et al., 2010). *Salmonella* was not found in cottage cheese samples that were purchased from retailers. The investigation revealed an overall *Salmonella* prevalence of 15.6% in raw and pasteurized milk samples collected from the surveyed regions (Bedassa et al., 2023). Raw milk had a larger percentage (19.7%), and pasteurized milk had a lower percentage (11.5%) of prevalence. The highest *Salmonella* prevalence (21.3%) was found in milk samples from collectors, while the lowest percentage (9.3%) was found in milk samples from retailers. Samples taken from producers had a greater prevalence of *Salmonella* (13.7%) than those taken from processors, but a lower prevalence (18.1%) than samples taken from collectors (Bedassa et al., 2023). Proteases and lipases are among the enzymes that *Salmonella* species can produce. While lipases break down the lipids in milk and dairy products to release fatty acids and produce off-flavors, proteases cause proteolysis, which results in a bitter flavor and gelation (Sobeih et al., 2020). This finally results in unwanted changes in the color, odor, pH, and taste of milk and dairy products (Sobeih et al., 2020). Dairy products and milk contaminated with *Salmonella* are unfit for human consumption due to their inferrior qualities (Sobeih et al., 2020).

6. Risk factors for contamination of milk with *Salmonella* species

The main causes of contamination of milk and dairy products with *Salmonella* species are; inadequate sanitation practices, inadequately designed facilities and equipment, poor maintenance, inadequate operational processes, inadequate production standards, and inadequate ingredient control (Bedassa et al., 2023; Sobeih et al., 2020).

6.1. Poor sanitation practices

A common contributing factor in many outbreaks of *Salmonella* infections is poor cleaning and sanitation (Nicolas et al., 2006). Dirty surfaces that come into contact with milk and dairy products may contaminate them with *Salmonella* (Nicolas et al., 2006). The prolonged survival of *Salmonella* on contaminated surfaces and its subsequent transmission to milk and dairy products significantly amplifies the risk of cross-contamination, particularly in environments lacking proper hygiene and sanitation standards (Nicolas et al., 2006). *Salmonella* Enteritidis can contaminate milk and dairy products from contaminated dry stainless steel surfaces (Sobeih et al., 2020). Studies have shown that *Salmonella* Enteritidis can be readily transferred from various surfaces to milk and dairy products, exhibiting transfer rates between 20% and 100% (Sobeih et al., 2020).

6.2. Poor facility, equipment design and inadequate maintenance

It is not always the case that faults in procedures and human performance result in cross-contamination due to sanitary practice failures. Sometimes the production equipment are not installed or maintained correctly, have poor hygienic design, or both. *Salmonella* contamination can also be a result of inadequate machinery maintenance and poor facility design (Nicolas et al., 2006). Following a statewide outbreak of *Salmonella* Typhimurium in the United States in 2008–2009, government inspectors found that the main origins of the bacteria were deficiencies in facility and equipment design, along with maintenance shortcomings in company processing factories (Reta et al., 2016; Teresiah et al., 2016).

6.3. Lack of good manufacturing procedures

Milk and dairy processors must be mindful of potential contamination threats and use good manufacturing procedures (GMPs) to completely protect their customers from *Salmonella* infections (Kiambi et al., 2022). Therefore, milk producers and processors must carefully assess their processes and practices, and implement the necessary mitigation measures based on the risks posed by their particular circumstances. To lower the danger of milk contamination, these precautions could include standard hygiene procedures during milking, storage, transit, and pasteurization. Additionally, extra caution should be exercised to prevent cross-contamination, which could result in the production of contaminated milk and dairy products. Incidences of *Salmonella* due to failed implementation of GMPs have been reported in Uganda (Wolff et al., 2017), Kenya (Nyokabi et al., 2021), Rwanda (Kamana et al., 2017), Ethiopia (Gebeyehu et al., 2022), Ghana (Parry-Hanson Kunadu et al., 2018) and India (Singh et al., 2018).

6.4. Poor ingredient control and handling

Even the most advanced equipment systems and rigorous operational protocols cannot fully mitigate cross-contamination if raw materials and ingredients are improperly selected, sourced, or managed (Paswan & Park, 2020). Incidences of *Salmonella* due to poor ingredient control and handling have been reported in countries such as Rwanda (Kamana et al., 2017), Ethiopia (Gebeyehu et al., 2022), Ghana (Parry-Hanson Kunadu et al., 2018), India, Uganda (Wolff et al., 2017) and Kenya (Nyokabi et al., 2021; Singh et al., 2018). Without a second kill phase, contaminated ingredients added to milk along the value chain might introduce *Salmonella* species (Paswan & Park, 2020). For example, some farmers add unboiled water to milk and dairy products prior to selling them yet the water may be contaminated with multiple serotypes of *Salmonella* including *S.* Abortusovis, *S.* Enteritidis, *S.* Infantis, *S.* Miami, *S.* Montevideo, *S.* Muenchen, *S.* Muenster, *S.* Paratyphi A, B and C, *S.* Poona, *S.* Sendai, *S.* Typhi, *S.* Thompson, *S.* Typhimurium, *S.* Anatum, *S.* Seftenberg, *S.* Newington, *S.* Oranienburg, and *S.* Habana (Paswan & Park, 2020).

6.5. Contamination due to failure to control pests

A key component of every milk processing facility is the capacity to manage pests. Common rodents and insects may act as *Salmonella* transmission vectors. Habana et al. (Paswan & Park, 2020) studied 48 rodents in a Japanese factory over a 1-year period, autopsied them, and then examined the contents of their stomachs. *Salmonella* was found in 46% of the rats that were found in the manufacturing area, but not in any of the rodents that were found in the receiving or storage sections (Lapuz et al., 2008). The rodents that tested positive for *Salmonella* contained *S.* Enteritidis, *S.* Montevideo, *S.* Muenchen, *S.* Muenster, *S.* Sendai, *S.* Typhi, *S.* Typhimurium and *S.* Newington as well as a number of unclassifiable isolates (Lapuz et al., 2008). It was revealed that *Salmonella* Montevideo was spread by insects such as cockroaches (Lapuz et al., 2008). It was discovered that cockroaches can acquire and spread *Salmonella* Typhimurium, making them potential vectors of the pathogen. Moreover, infected cockroaches could spread the pathogen to other cockroaches. Because of their mobility, rodents and insects could readily help to spread *Salmonella* from a previously isolated niche throughout the dairy processing facility (Lapuz et al., 2008). Contamination due to failure to control pests has been reported in Ethiopia (Gebeyehu et al., 2022), Ghana (Parry-Hanson Kunadu et al., 2018) and India (Singh et al., 2018). However, pests in dairy processing facilities can be controlled by cleaning both the interior and exterior of all equipment, utilizing electrified grids to deter pests. Rats and mice can be effectively controlled by use of bait stations and mouse traps. Ultraviolet (UV) light in fly catchers can be used to attract and trap pests like flies and mosquitoes (Singh et al., 2018).

7. Use of antibiotics in dairy production

Antibiotics are a class of antimicrobial compounds that may originate from natural sources or be produced through artificial synthesis. They are capable of either suppressing the growth of or completely eradicating bacterial pathogens (Alves et al., 2020). Antibiotics are used as growth promoters in modern dairy production, either directly or indirectly, to prevent and treat disease and preserve milk and other dairy products (Sobeih et al., 2020). Studies on the availability of antibiotics for animal therapy in Ethiopia indicated that a large percentage of farmers (80.9%) had access to them but 64.4% were untrained in their handling and use (Babio et al., 2015). Therefore, dairy farmers relied on medication merchants, pharmacy (41.1%), veterinary doctors (48.2%), and cattle markets (2.7%) for usage instructions

(Babio et al., 2015). Some of the common classes of antibiotics used in the dairy value chain to manage salmonellosis include: Tetracycline, Aminoglycosides, Cephalosporins, Quinolones, Sulfonamides, Chloramphenicol, Sulfadimidine, and Sulfamethoxazole (Alexander et al., 2009; Odoch et al., 2018). However, these antibiotics are sometimes irrationally applied which leads to emergence of several antibiotic-resistant bacteria including of *Salmonella*; these usually find their way into the milk and processed dairy products that are consumed by humans (Sobeih et al., 2020). Antibiotic resistance of *Salmonella* in milk and dairy products has been reported in Kenya (Nyokabi et al., 2021), Rwanda (Kamana et al., 2017), Ethiopia (Gebeyehu et al., 2022), Ghana (Parry-Hanson Kunadu et al., 2018) and India (Singh et al., 2018).

7.1. Antibiotic resistance of Salmonella species in the dairy value chain

Antibiotic resistance is acknowledged as a global health challenge (Alexander et al., 2009; Odoch et al., 2018). About 10 years ago from 2013, the prevalence of antibiotic-resistant *Salmonella* in the global dairy value chain drastically increased (Asefa et al., 2023; Bedassa et al., 2023). Improvident use of antibiotics at different stages along the dairy value chain represents the primary driver of antibiotic resistance in *Salmonella* species (Virto et al., 2022). Antibiotic-resistant strains of *Salmonella* usually find their way into the milk, feces, feeds, meat, and later into humans, water, soil, plants, and other animals (Li and Webster, 2018; Murray et al., 2022). Antibiotic-resistant *Salmonella* species are currently a serious global public challenge as treatment for the majority of *Salmonella*-caused infections in humans and animals has become more difficult (Dadgostar, 2019; Sabtu et al., 2015). *Salmonella* Enteritidis and *Salmonella* Typhimurium have progressively emerged as the predominant cause of salmonellosis throughout countries at varying levels of economic development (Virto et al., 2022; Wang et al., 2020). For instance, when 17 different antimicrobial agents were examined against 14 *Salmonella* isolates from 350 raw cows' milk samples in Iran, 11 isolates (78.57%) exhibited resistance to Nalidixic acid (30 µg), 3 isolates (21.42%) were resistant to Cephalothin (20 µg), Neomycine (30 µg), Choloramphenicol (30 µg) and 6 isolates (42.58%) were resistant to Ampicillin (10 µg) and Tetracycline (30 µg) (McEvoy et al., 2003). Out of the 14 isolates, only 3 isolates were resistant to Nalidixic acid, Cephalotin, Ampicilin, Streptomycine, Neomycin, Choloramphenicol, and Tetracyclin (McEvoy et al., 2003). In Ethiopia, 10.7% (21 out of 195) of the dairy cows contained *Salmonella* that is 100% resistant to ampicillin and 83% resistant to two or more antibiotics (Addis et al., 2011). The majority of the *Salmonella* isolates showed a comparatively high sensitivity to chloramphenicol, ciprofloxacin, and cotrimoxazole (Addis et al., 2011). In addition, analysis of 120 samples comprising fresh milk, yogurt, and cotton swabs from milk containers and cups in Ethiopia resulted in the isolation of 80 bacterial strains, of which 7.8% were identified as *Salmonella* spp (Virto et al., 2022; Wang et al., 2020). Fresh milk and yogurt had a higher rate of contamination (28.1%). Every isolate was resistant to at least one of the examined antibiotics (Virto et al., 2022; Wang et al., 2020). A cross-sectional study was carried out between December 2021 and May 2022 to assess the prevalence of *Salmonella* in raw milk obtained from Areka town, Boloso Sore Woreda, and the Wolaita Zone in Southern Ethiopia (Asefa et al., 2023). In a total of randomly collected 151 direct udder milk samples, the prevalence of *Salmonella* was 9.3% (14 out of 151) (Asefa et al., 2023). Currently, the prevalence of *Salmonella* in Ethiopia is 8.54, 12.69, and 10.46% in Hawassa, Dale, and Arsi Negele districts, respectively (Asefa et al., 2023). The study found no statistically significant variation in bacterial prevalence among the districts ($p > 0.05$). It further revealed that *Salmonella* isolates were entirely susceptible to ciprofloxacin yet exhibited complete resistance to ampicillin, with all isolates demonstrating multi-drug resistance (MDR) (Asefa et al., 2023). In another study, all 159 popular dairy products obtained from five traditional milk markets in Accra, Ghana, were found to be contaminated with *Salmonella* (Parry-Hanson Kunadu et al., 2018). The isolates were also resistant to 18 different antibiotics (Parry-Hanson Kunadu et al., 2018). *Salmonella enterica* serotypes Muenster and Legon that are multidrug resistant were found in 11.8% and 5.9% of samples of unfermented cheese, respectively. Trimethoprim/Sulfamethoxazole, Cefoxitin, Cefuroxime Axetil, and Cefuroxime were all ineffective against any *Salmonella* strain. Resistance was detected to the first-choice antibiotic therapies administered in Ghana for treating NTS bacteremia, with 18% of isolates resistant to chloramphenicol and 100% resistant to ciprofloxacin (Parry-Hanson Kunadu et al., 2018).

Table 5. Antimicrobial resistance profiles of *Salmonella enterica* isolates from bulk tank milk in the United States (Parry-Hanson Kunadu et al., 2018).

	Resistant isolates	
Antimicrobial agent	Number of resistant isolates	Percentage (%)
Amikacin	0	0.00
Amoxicillin–clavulanic acid	20	11.36
Ampicillin	23	13.07
Cefoxitin	20	11.36
Ceftiofur	20	11.36
Ceftriaxonel	20	11.36
Chloramphenicol	23	13.07
Ciprofloxacin	0	0.00
Gentamicin	0	0.00
Kanamycin	12	6.82
Nalidixic acid	0	0.00
Streptomycin	27	15.34
Sulfisoxazole	25	14.20
Tetracycline	27	15.34
Trimethoprim-sulfamethoxazole	0	0.00

Table 6. Antimicrobial susceptibility patterns of *Salmonella* isolates recovered from raw cow milk samples collected in Southern Ethiopia (Gebeyehu et al., 2022).

	Antimicrobial susceptibility profile of the isolates		
Tested antibiotics	Resistance (%)	Intermediate susceptibility (%)	Susceptibility (%)
Ampicillin	40 (100)	–	–
Cefotaxime	31 (77.5)	3 (7.5)	6 (15.0)
Chloroamphenicol	10 (25.0)	17 (42.5)	13 (32.5)
Ciprofloxacin	–	–	40 (100)
Gentamycin	17 (42.5)	13 (32.5)	10 (25.0)
Kanamycin	26 (65.0)	11 (27.5)	3 (7.5)
Nalidixic Acid	–	23 (57.5)	17 (42.5)
Streptomycin	37 (92.5)	3 (7.5)	–
Trimethoprim & Sulphamethaxazole	9 (22.5)	0 (0.0)	31 (77.5)

7.2. Control of antibiotic-resistant Salmonella

Antimicrobial-resistant infections attributable to *Salmonella* species usually have limited treatment options (Asefa et al., 2023). When treating infections caused on by antibiotic-resistant *Salmonella*, medical practitioners mainly utilize carbapenems (antibiotics of last resort). Furthermore, because using lytic phages as biocontrol agents has so many benefits, using them to biocontrol *Salmonella* in the food industry has grown in popularity. As natural substitutes for conventional antimicrobial treatments, phages have been successfully used to control bacterial infections in the food sector, facilitating the emergence of several phage-derived products (Parry-Hanson Kunadu et al., 2018). The food industry can stop food products like milk and dairy products from microbial spoilage by treating them with particular phages. Moreover, effective antimicrobial use is vital for controlling the transmission of bacterial diseases, ultimately fostering safe conditions for food production, processing, and handling across both plant and animal systems (Parry-Hanson Kunadu et al., 2018).

The antibiotic resistance profiles of *Salmonella enterica* isolates from bulk tank milk in the United States showed that resistance to tetracycline and streptomycin, each at 15.34%, were the most commonly observed among the 15 antimicrobial agents tested. This was followed by Sulfisoxazole (14.20%), ampicillin (13.07%), chloramphenicol (13.07%), amoxicillin–clavulanic acid (11.36%), cefoxitin (11.36%), ceftiofur (11.36%), ceftriaxone (11.36%), and kanamycin (6.82%). Amikacin, ciprofloxacin, gentamicin, nalidixic acid, and trimethoprim-sulfamethoxazole demonstrated efficacy against all isolates (Table 5).

Nine commonly used antimicrobials were tested against 40 *Salmonella* isolates obtained from raw cow milk samples collected in Southern Ethiopia. Results showed that every isolate exhibited resistance to at least one of the tested antimicrobial agents. High resistance rates were observed for ampicillin (100%), streptomycin (92.5%), and cefotaxime (72.5%). Conversely, all isolates were fully susceptible to ciprofloxacin (100%), and 77.5% were susceptible to trimethoprim-sulfamethoxazole (Table 6).

7.3. *Transmission of antibiotic-resistant Salmonella species in the dairy value chain*

Antibiotic-resistant *Salmonella* species are selected, propagated, and disseminated throughout the dairy value chain primarily as a result of the irrational use of antibiotics in dairy production (Alexander et al., 2009; Odoch et al., 2018). Transmission of these species to milk and dairy products usually occurs directly through animal feeds and water (Figure 2). Milk and dairy products that have been contaminated with antibiotic-resistant *Salmonella* species cause the gut microbiota to acquire antibiotic resistance genes (Figure 2). Following host colonization, antibiotic-resistant *Salmonella* strains have the potential to transfer resistance genes to other intestinal microbiota via mobile genetic elements, including phages, transposons, and plasmids (Johansson et al., 2021). Both horizontal and vertical gene transfer can take place simultaneously. Resistance genes are exchanged between different bacterial species via horizontal gene transfer, while within the same species, these genes are transmitted through vertical gene transfer (Johansson et al., 2021).

8. Types of antibiotic resistance exhibited by *Salmonella* species

Systematic antibiotic surveillance systems for detection of antibiotic-resistant *Salmonella* spp. are uncommon especially in developing countries due to capacity limitations. However, like many other bacterial species, it has been reported that *Salmonella* species also exhibit several antibiotic resistance types as explained below;

8.1. *Intrinsic antibiotic resistance*

Salmonella species have the innate ability to resist antibiotics which leads to intrinsic resistance (Reygaert, 2018). Because of their natural structural and functional properties, some *Salmonella* species are not

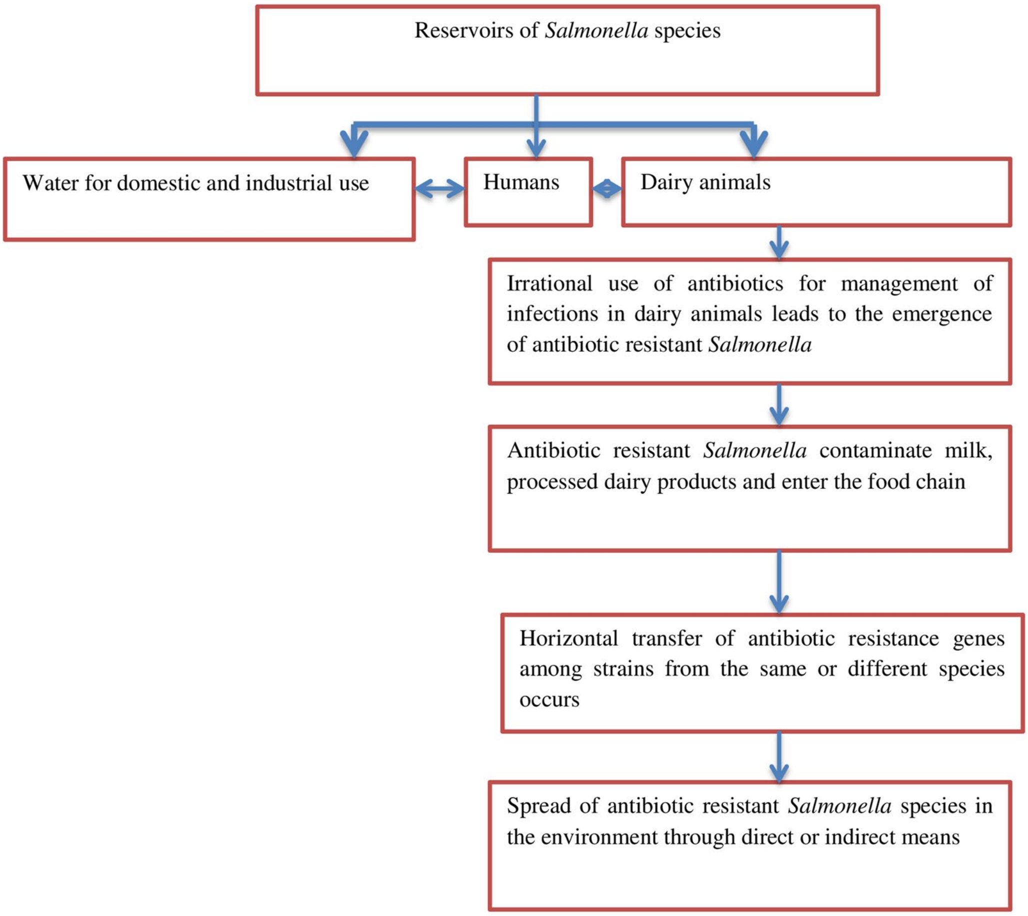

Figure 2. A flow chart showing spread of antibiotic-resistant *Salmonella* species in the diary value chain (Wang et al., 2020).

susceptible to and do not respond to specific classes of antibiotics (Reygaert, 2018). The mechanisms underlying intrinsic antibiotic resistance include the absence of the antimicrobial's target site within the bacterium, restricted drug penetration due to cell impermeability, active efflux via chromosomally encoded transporters, and the innate ability to synthesize drug-inactivating enzymes (Reygaert, 2018). For instance, the outer membrane of *Salmonella* species prevents the entry of Penicillin and majority of beta-lactams as well as larger molecule size antibiotics such as Bacitracin and Vancomycin (Kong et al., 2010). Normal intrinsic resistance is characteristic of specific bacterial species or genera and is transmitted exclusively through vertical inheritance, without the capacity for horizontal gene transfer to unrelated bacteria (Kong et al., 2010).

8.2. Acquired antibiotic resistance

When microorganisms become resistant to antibiotics that they were previously susceptible or sensitive to, this is known as acquired antibiotic resistance (Aminov, 2010; Aslam et al., 2018; Manyi-Loh et al., 2018). Following the advent of antibiotic therapy, microorganisms have progressively developed diverse acquired resistance mechanisms, enabling them to survive antimicrobial exposure (Aminov, 2010). The emergence of this resistance is primarily attributed to genetic modifications, either through mutation or via horizontal gene transfer (HGT) involving mobile genetic elements such as plasmids, transposons, and phages (von Wintersdorff et al., 2016). The principal mechanisms facilitating horizontal gene transfer (HGT) include conjugation, transformation, and transduction, each enabling the exchange of genetic material between bacterial cells (Aminov, 2010).

Conjugation is the exchange of mobile DNA components between two bacterial cells; it necessitates close physical contact between the donor and the recipient cells (Reygaert, 2018). Conjugation causes the spread of genes encoding for antibiotic resistance and is the main factor contributing to expansion of antibiotic resistance (von Wintersdorff et al., 2016). Mobile genetic elements, especially plasmids, play a key role in the conjugative transfer of antibiotic resistance genes among *Salmonella* species (von Wintersdorff et al., 2016). The process of transformation is the assimilation of bare or extracellular donor DNA (Reygaert, 2018). As transformation needs homology between the DNA of the donor and recipient, the process can only happen between *Salmonella* species that are closely related (von Wintersdorff et al., 2016). The recipient cell's chromosomes include donor DNA that has been integrated into them (von Wintersdorff et al., 2016).

By natural and artificial gene alterations, acquired resistance can also be transmitted vertically. *Salmonella* species have developed a variety of non-exclusive resistance mechanisms, and interaction between several mechanisms can lead to high level resistance (Chen et al., 2021; von Wintersdorff et al., 2016). Resistance across all principal antibiotic classes, including beta-lactams, sulfonamides, macrolides, aminoglycosides, tetracyclines, quinolones, chloramphenicol, and fluoroquinolones, has been identified in isolates from milk and dairy products in Egypt, Ethiopia, Kenya, and India (Aslam et al., 2018; Li & Webster, 2018; El-Sharkawy et al., 2017).

8.3. Mobile genetic elements and acquired antibiotic resistance in Salmonella

Any section of DNA that can move from one region of the genome to another is known as mobile DNA (Pei et al., 2020). Horizontal gene transfer (HGT) is primarily mediated by a variety of mobile genetic elements, including plasmids, integrative and conjugative elements (also known as conjugative transposons), insertion sequences, bacteriophages through transduction, mobile introns, and integrons (Pei et al., 2020). Mobile genetic elements (MGEs), which are crucial in spreading antibiotic resistance, serve as vectors facilitating the acquisition and transfer of antibiotic resistance genes (ARGs) from environmental reservoirs to pathogens that infect humans and animals (Pei et al., 2020).

Extra-chromosomal circular DNA molecules known as plasmids can multiply on their own, separate from the cells' chromosomes. Some plasmids carry genes for antibiotic resistance and virulence factors; however these genes are not necessary for the host bacterial survival (Rozwandowicz et al., 2018). Conjugative plasmids are plasmids that have genes for conjugation, while mobilizable plasmids are plasmids that have an origin of transmission (von Wintersdorff et al., 2016). *Salmonella* plasmids can be transferred to different species of bacteria depending on their host range. However, certain plasmids can only be transferred to members of the same species or genus. DNA fragments known as integrative and conjugative elements, commonly referred to as conjugative transposons, can move around an organism's genome (Rozwandowicz et al., 2018). During chromosomal replication and cell division, they passively spread after being integrated into the host genome (Rozwandowicz et al., 2018).

Salmonella genetic components known as integrons facilitate the movement of smaller mobile elements known as gene cassettes (von Wintersdorff et al., 2016). These are not truly mobile elements because only the gene cassettes are mobile. According to their *intI* gene, at least six kinds of integrons have been identified in *Salmonella* (von Wintersdorff et al., 2016). Among integron classes, classes 1, 2, and 3 have been the focus of considerable research due to their prominent involvement in the dissemination of antibiotic resistance genes (Kong et al., 2010; Pei et al., 2020; Rozwandowicz et al., 2018).

9. Mechanisms of antibiotic resistance exhibited by *Salmonella* species

Salmonella species have developed a number of antibiotic resistance mechanisms (Table 7). Membrane impermeability, antimicrobial agent inactivation, active antimicrobial agent export from the cell, the development of biofilms (Yuan et al., 2018). *Salmonella* species can also alter the antibiotic target sites to prevent the antibiotic from binding on the target sites (Yuan et al., 2018). (Table 1). The dissemination of resistance genes among certain *Salmonella* species leads to the emergence of resistance against antibiotics that were previously effective (Chen et al., 2021; von Wintersdorff et al., 2016).

Reduced cellular porin expression and porin gene mutations reduce inflow of antibiotics, resulting in a cell wall that is less permeable to antibiotics (Li & Webster, 2018; Sabtu et al., 2015). Tetracycline, Beta-lactams, and Chloramphenicol are only a few examples of the antibiotics that are taken up by the outer membrane porins (OMP). Enhanced antibiotic efflux mediated by overexpressed or mutated genes encoding multidrug-resistant efflux pumps belonging to extensive protein families is a key mechanism underlying antibiotic resistance (Chen et al., 2021; von Wintersdorff et al., 2016).

The five identified superfamilies of efflux pumps include the ATP-binding cassette (ABC) family, the small multidrug resistance (SMR) family, the major facilitator superfamily (MFS), the resistance-nodulation-division (RND) family, and the multidrug and toxic compound extrusion (MATE) family (Kim et al., 2021). Target modifications mostly take place through chemical and mutational changes, target site protection, substitution of functionally comparable but insensitive targets for sensitive ones, and overproduction of sensitive targets (Kim et al., 2021). The DNA gyrase genes topoisomerase II and topoisomerase IV undergo changes when *Salmonella* spp develop Fluoroquinolone resistance, which shields the cellular targets from antibiotic actions in an area known as the quinolone resistance determining region (Blair et al., 2015). After the antibiotic has entered the bacteria, it may be altered through enzymatic breakdown such that it loses the ability to attach to the intended target (Blair et al., 2015). A modification in enzymes, such as those found in acetyltransferases is another mechanism that bacteria use to resist against antibiotics (Chen et al., 2021; von Wintersdorff et al., 2016).

Table 7. Mechanisms used by *Salmonella* spp to resist against various classes of antibiotics (Alexander et al., 2009).

Antibiotic class	Mechanism of action	Mechanism of resistance
Aminoglycosides	Inhibit membrane protein synthesis by binding to the P10 protein within the 30S ribosomal complex	Modification of enzymes
Cephalosporins	Inhibit enzymatic reactions essential for stable cell wall synthesis by binding to penicillin-binding proteins (PBPs)	Altered membrane permeability; enzyme modification through beta-lactamases; and alteration of target sites such as penicillin-binding proteins (PBPs).
Chloramphenicol	Inhibit protein synthesis by binding to the 50S ribosomal subunit, thereby blocking transpeptidation	Enzyme modification mediated by chloramphenicol transacetylase
Quinolones	Bind to topoisomerase II, blocking DNA replication, and also bind to topoisomerase IV, interfering with the separation of interlinked replicated DNA molecules	Alterations of target sites due to mutations in topoisomerase II or IV, coupled with active efflux systems.
Sulfonamides	Inhibit folic acid synthesis	Target site insensitivity
Tetracycline	Inhibit protein synthesis by binding to the 30S ribosomal subunit, preventing the attachment of aminoacyl-tRNA to the mRNA-ribosome complex	Active export via efflux mechanisms.
Trimethoprim- Sulfamethoxazole	Sequentially interfere with folic acid synthesis	Reduced permeability and target site insensitivity

Table 8. Mechanisms used by *Salmonella* spp to resist against heat (Farakos et al., 2013; Yuan et al., 2018).

Mechanism	Description
Heat Shock Proteins (HSPs)	*Salmonella* produces heat shock proteins (DnaK, GroEL, and ClpB) in response to temperature stress, which help the bacteria to refold denatured proteins and protect cellular structures during heat exposure.
Membrane Fluidity Adjustments	*Salmonella* adjusts the composition of its cell membrane, such as increasing the production of unsaturated fatty acids, to maintain membrane integrity at high temperatures.
Thermotolerance via Sigma Factors	Alternative sigma factors (e.g. RpoS) regulate the expression of genes that confer heat tolerance, such as those involved in stress response, nutrient uptake, and membrane repair.
Biofilm Formation	*Salmonella* can form biofilms, which provide a physical barrier that protects the bacteria from environmental stresses, including heat.
Quorum Sensing	*Salmonella* uses quorum sensing to coordinate stress responses, including heat shock, through the production of signaling molecules (autoinducers) that regulate gene expression.
Accumulation of Compatible Solutes	*Salmonella* can accumulate compatible solutes (e.g. trehalose, glycerol) that stabilize proteins and cellular structures during thermal stress.
Heat-induced Mutation	High temperatures may increase mutation rates in *Salmonella*, which can lead to the selection of more heat-resistant variants over time.

Enzymes produced by bacteria change antibiotics chemically during enzymatic modifications. This can be accomplished by attaching acetyl, adenyl, or phosphate groups to particular antibiotic molecules (Chen et al., 2021; von Wintersdorff et al., 2016). This process is frequently used in Macrolides, Aminoglycosides, and Phenicols (Chen et al., 2021; von Wintersdorff et al., 2016). Enzymatic inactivation occurs when bacteria secrete enzymes that bind to the antibiotic directly and break it down. Enzymatic inactivation of Penicillins, Cephalosporins, Monobactams, and/or Carbapenems has been reported in *S.* Enteritidis and *S.* Typhimurium isolated from raw milk in Ethiopia (Bush, 2010).

10. Mechanisms used by *Salmonella* to resist against heat

Salmonella, like other bacteria, can endure various environmental stresses, including heat (Farakos et al., 2013; Yuan et al., 2018). Such adaptability facilitates the persistence and proliferation of the organism under various conditions, notably within food processing settings. Heat resistance in *Salmonella* involves a combination of genetic, molecular, and physiological mechanisms (Farakos et al., 2013; Yuan et al., 2018). These mechanisms enable the bacteria to either withstand or repair heat-induced damage.

Salmonella uses various mechanisms to resist against heat. Such mechanisms include; production of heat shock proteins, Quorum Sensing, DNA repair systems, changes to membrane composition, protein synthesis regulation, biofilm formation, osmotic stress responses, and heat-induced mutation (Table 8).

11. Effectiveness of heat treatment in control *Salmonella* in the dairy value chain

In food processing, heat treatment is widely used to minimize or completely eliminate pathogenic bacteria in order to prevent food spoilage and transmission of foodborne diseases (Chiozzi et al., 2022). The inherent diversity of microorganisms with regard to their resistance to heat poses a great challenge to the effectiveness of using heat to control them (Den Besten et al., 2018). Controlling the pathogens and avoiding cross-contamination and recontamination increases the safety of milk and dairy products (Owusu-Kwarteng et al., 2020). To get rid of the microorganisms in the tainted milk, heat treatment is required. A number of thermal treatment techniques, including steam, moist and dry hot air, can increase food safety (Chiozzi et al., 2022).

Thermal processing techniques such as dry heat, wet heat, and electromagnetic radiation are effective in significantly reducing pathogen load in milk (Chiozzi et al., 2022). Hot air exposure and superheated steam are examples of dry heat treatments. Utilizing wet heat, controlled condensation steam and moist air impingement can eliminate microorganisms from milk and dairy products (Podolak et al., 2010). Compared to conventional methods, radiofrequency, infrared, and microwave radiation are successful at heating milk more quickly (Den Besten et al., 2018). Nonetheless, some bacterial pathogens, including *Salmonella*, exhibit heat resistance that enables them to withstand thermal processing, increasing the risk of foodborne illness among consumers of milk and dairy products (Den Besten et al., 2018).

Currently, thermal processing remains the most effective and widely used technique for eliminating microorganisms from milk and dairy products (Xiong et al., 2020). Mathematical models are essential to the efficient design of thermal processing in order to guarantee product safety (Xiong et al., 2020). To effectively apply predictive models, it is essential to conduct thermal resistance studies to determine the thermal death parameters of the relevant pathogen(s) (Xiong et al., 2020). In China, research on *Salmonella* in peanut butter revealed that the presence of oil was a key factor contributing to the pathogen's exceptional heat tolerance and its nonlinear thermal inactivation behavior (Ma et al., 2009). Likewise, the elevated fat content in milk and dairy products has been demonstrated to increase the heat resistance of *Salmonella* within these food matrices (Ma et al., 2009).

12. Factors that affect the heat resistance of *Salmonella* species

Knowledge of the target pathogens' heat resistance in foods is essential for designing effective thermal processing technologies (Den Besten et al., 2018). Multiple factors related to both the food product and processing conditions such as water activity, water mobility, and the intrinsic properties and composition of the food affect the thermal resistance of pathogenic microorganisms (Den Besten et al., 2018). Heat resistance is also influenced by factors relating to the microorganisms, including strain, development circumstances, age, quantity and number of bacterial cells (Den Besten et al., 2018). The following subsections concentrate on the primary product-related elements linked to pathogens' heat resistance in foods.

12.1. Water activity and thermal resistance properties of among Salmonella species

The amount of moisture in milk and its products greatly affects the ability of *Salmonella* to withstand heat. Various studies have revealed that *Salmonella* species are dangerous pathogens that can contaminate low-moisture food products. In food preservation, one of the most important factors is water activity. Water activity refers to the difference between a food system's water vapor pressure (Pv) and saturation Pvs at the same temperature (Syamaladevi et al., 2016). Water activity, which refers to the extent to which water can escape from food, is fundamentally a thermodynamic property (Syamaladevi et al., 2016). In the context of food manufacturing, water vapor can reasonably be considered an ideal gas, allowing water activity to be approximated by the ratio of the fugacity of water in the food to that of pure liquid water, which serves as the reference state (Syamaladevi et al., 2016). When food is in thermodynamic equilibrium within a closed system, the vapor pressure of water in the food or in a component of a multi-component food system matches that of water in the surrounding air (Syamaladevi et al., 2016). Additionally, water activity can be expressed in terms of the chemical potential of water, representing the partial molar free energy of water within the food system (Syamaladevi et al., 2016).

The heat resistance of *Salmonella* tends to increase when the water activity (aw) of a food system drops below 0.6 (Syamaladevi et al., 2016). At such low aw levels, the reduction in cellular water content can sometimes lead to the stabilization of protein structures, helping protect microbial cells from heat-induced denaturation (Mañas & Pagán, 2005). As early as the late 1960s, researchers recognized that water activity plays a critical role in influencing the thermal resistance of microorganisms in low-moisture food environments (Syamaladevi et al., 2016).

Figure 3 illustrates that vegetative cells of foodborne pathogens, along with bacterial and fungal spores, can persist for extended periods in foods and ingredients with water activity levels below 0.85 (Paswan & Park, 2020). A recent study using skim milk powder demonstrated that water activity (aw) significantly influences the survival of *Salmonella enterica* (Yuan et al., 2018). Notably, microbial survival was considerably greater at aw 0.33 compared to aw 0.53 and aw 0.81, with statistical significance ($p < 0.05$) (Yuan et al., 2018). This was reflected in the reduction rates of viable cell counts after 2 months of storage at 37 °C, which were 4.23, 4.69, and 5.85 log CFU/g for aw levels of 0.33, 0.53, and 0.81, respectively. (Yuan et al., 2018).

12.2. Water mobility

Unlike water activity, which represents a macroscopic thermodynamic property, water mobility refers to the molecular-level movement of water, including translational, rotational, and vibrational motions within

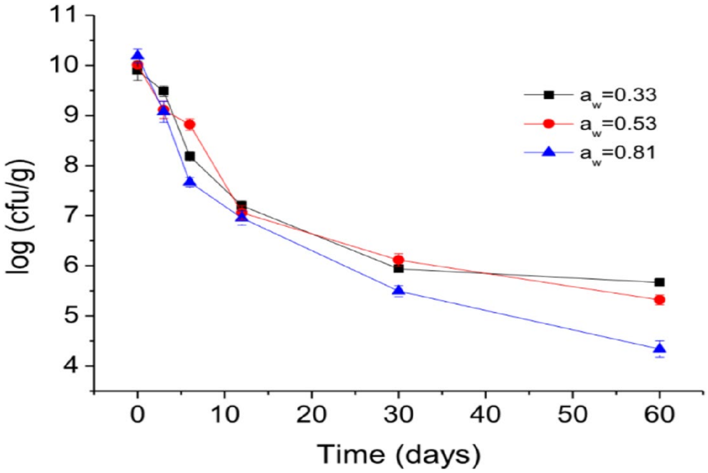

Figure 3. Survival of *Salmonella enterica* at 37 °C across three different water activity levels during 2 months of storage in skim milk powder (Paswan & Park, 2020).

food systems (Syamaladevi et al., 2016). Through self-diffusion, water molecules can move translationally in three-dimensional space (Faraone et al., 2003). Techniques including nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) spectroscopy are effective for quantifying molecular motion in both liquid and vapor phases (Faraone et al., 2003). MRI, grounded in the principles of NMR, allows for the detailed observation of molecular behavior based on the absorption and emission of radiofrequency energy within the electromagnetic spectrum (Faraone et al., 2003). Rotational motion where a water molecule spins around its axis is more pronounced in the liquid and vapor phases compared to the solid state while vibrational motion arises from stretching, bending, or spinning of the molecule's bonds (Faraone et al., 2003). In non-equilibrium systems like food matrices, water molecules remain mobile, and this mobility influences the availability of water for microbial growth and survival (Faraone et al., 2003; Syamaladevi et al., 2016). Studies have shown that *Salmonella* Typhimurium, *S.* Tennessee, *S.* Agona, and *S.* Montevideo isolated from whey protein powder were able to persist across water activity values ranging from 0.19 to 0.54, and temperatures between 21 °C and 80 °C. (Farakos et al., 2013) Notably, the survival of these *Salmonella* serotypes was significantly affected by water activity, with higher survival observed at lower aw levels (Farakos et al., 2013). This reduced water mobility in low-moisture foods such as powdered milk greatly enhances the thermal resistance of *Salmonella* during heat processing (Farakos et al., 2013).

12.3. Composition of food products

The chemical composition of food matrices such as carbohydrate-, protein, or fat-rich systems plays a significant role in determining the thermal resistance of microorganisms (Farakos et al., 2013; Syamaladevi et al., 2016). Solutes like glycerol, sucrose, and sodium chloride affect how resistant microorganisms are to heat, which is likely due to the media's decreased aw (Coroller et al., 2001). At equivalent water activities of 0.75, 0.80, and 0.90, sucrose confers more effective thermal protection to *Salmonella* in tryptic soy broth than sodium chloride or glucose-fructose during heat treatments conducted between 55 °C and 72 °C (Coroller et al., 2001).

The D-values of Salmonella vary from 26.5 to 30.6 minutes at 71 °C, and from 8.6 to 13.4 minutes at 90 °C (Ma et al., 2009). After being heated at 75 °C for 25 to 50 minutes, *Salmonella* spp survive longer and at a lower aw (0.3 vs. 0.6) (Kataoka et al., 2014).

12.4. Microbiological factors

An organism's ability to withstand heat is influenced by multiple factors, including its species, growth conditions, the presence of competing microflora, composition of the growth medium (such as levels of calcium, magnesium, iron, or fatty acids), and the temperature at which it was cultivated

(Moura-Alves et al., 2020). For instance, *Salmonella* Senftenberg and *S.* Bedford, when grown to the stationary phase and recovered on peptone-Lemco agar supplemented with oxalated horse blood after incubation for 48 hours at 37 °C, exhibited D-values at 55 °C of 36.2 and 18.8 minutes, respectively (Moura-Alves et al., 2020). Heat inactivation of microorganisms occurs through several mechanisms, including protein unfolding and denaturation, damage to ribosomal components, and inactivation of essential enzymes (Ahnoff et al., 2015). Research has shown that in high-moisture environments, the primary cause of bacterial cell death due to heat is the irreversible destabilization of ribosomal subunits, particularly the 30S and 50S units (Ahnoff et al., 2015). For example, the z-value of *S.* Senftenberg in milk chocolate has been reported as 18 °C (Ahnoff et al., 2015). In low-moisture conditions, desiccation of bacterial cells significantly reduces molecular mobility, thereby stabilizing ribosomal structures and protecting them from heat-induced irreversible damage (Ahnoff et al., 2015). *Salmonella* can persist in low-moisture foods for extended periods by employing several survival strategies, including biofilm formation, filamentation, entry into a viable but non-culturable state, and the synthesis of osmoprotectants such as betaine and proline (Finn et al., 2013). Moreover, under stress conditions such as low water activity and elevated temperatures, *Salmonella* activates specific stress response genes like rpoS to facilitate rapid adaptation to the adverse environment (Finn et al., 2013).

A recent study investigating the heat resistance of *Salmonella* and the effects of storage in non-fat dried milk revealed that a cocktail of *Salmonella* strains (*S.* Senftenberg 775 W, *S.* Typhimurium TM1, and *S.* New Brunswick 1608) exhibited remarkable resistance to dry heat when suspended in non-fat dry milk powder containing 4% moisture (Mercer et al., 2015). Notably, even prolonged exposure to dry heat at 60 °C or 76.6 °C for 10 hours failed to inactivate the Salmonella cells (Table 9) (Mercer et al., 2015). Moreover, attempts to eliminate *Salmonella* in the 4% moisture milk powder by subjecting it to dry heat at 85 °C for 2 hours or at 115.5 °C for 45 minutes were also unsuccessful (Mercer et al., 2015). However, applying excessively high temperatures, such as 115 °C for 1 hour, not only failed to ensure microbial inactivation but also compromised the quality of the product, resulting in a burnt yellow appearance (Table 9) (Mercer et al., 2015).

Additional research has shown that *Salmonella* and other foodborne bacteria can survive for extended periods in powdered milk and may resume growth once the product is reconstituted and stored under favorable conditions (Canning & Date, 2020; Syamaladevi et al., 2016). Storage of *Salmonella*-contaminated milk powder at different temperatures over 15 weeks did not result in a significant reduction in viable cells (Dega et al., 1972). Although elevated storage temperatures may contribute to microbial reduction, they often degrade the product's flavor quality (Farakos et al., 2013). The ability of *Salmonella* to survive drying is further enhanced by increased moisture content and water activity (aw), both of which contribute to its thermal resistance (Dega et al., 1972; Farakos et al., 2013). The persistence of viable *Salmonella* cells in dried milk was confirmed even after 10 hours at 76.6 °C (Dega et al., 1972; Farakos et al., 2013).

13. Future prospects

Future research on antibiotic and heat-resistant *Salmonella* species in the dairy value chain should focus on identifying the source of antibiotic and heat-resistant *Salmonella* species as well as the extent to

Table 9. Survival of *Salmonella* in non-fat dried milk containing 4% moisture when exposed to dry heat (Paswan & Park, 2020).

	Survival *Salmonella* count (CFU) at temperature (°C)			
Exposure time	60	76.6	85	115.5
0	6.9×10^5	7.3×10^5	9.4×10^4	9.4×10^4
15 min	5.4×10^5	ND	ND	1.6×10^4
30 min	4.5×10^5	1.35×10^5	7.1×10^3	8.0×10^2
45 min	ND	ND	ND	2.0×10^1
1 h	4.7×10^5	4.5×10^4	8.7×10^2	<1
2 h	3.0×10^5	5.0×10^4	3.5×10^2	<1
3 h	3.8×10^5	3.0×10^3	8.0×10^1	<1
4 h	ND	2.9×10^3	5.0×10^1	<1
5 h	3.0×10^5	1.4×10^3	2	<1
10 h	4.0×10^3	3.2×10^2	<1	<1

which milk producers and handlers especially in developing countries are aware of milk quality and best dairy practices. To advance research on antibiotic and heat resistance, there is a critical need for the development or availability of cost-effective, straightforward, and rapid screening methods that yield accurate, reliable, and reproducible results. To understand the mechanisms underlying heat resistance of *Salmonella*, more research on their survival mechanisms should be conducted. These will help in creating mitigation measures for controlling heat-resistant *Salmonella* species hence reducing the risk to public health and economic burdens caused by the presence of these organisms in the dairy value chain.

14. Conclusion

Salmonella contamination presents a significant challenge to the dairy sector globally, with developing countries such as Ethiopia, Ghana, Kenya, and Uganda being particularly vulnerable. Contamination is more frequently reported in raw milk than in processed dairy products. The most commonly identified *Salmonella* serotypes along the dairy value chain include *S.* Enteritidis, *S.* Montevideo, *S.* Paratyphi A, B, and C, *S.* Sendai, *S.* Typhi, *S.* Typhimurium, and *S.* Newington. These serotypes have demonstrated resistance to various antibiotics and thermal treatments through multiple mechanisms, posing a considerable challenge to dairy safety and quality. Addressing this issue requires targeted interventions in hygiene practices, surveillance, and control strategies throughout the dairy production and supply chain.

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Authors' contributions

CRediT: **Amos Mugabe**: Conceptualization, Funding acquisition; **Ediriisa Mugampoza**: Supervision, Validation, Writing – review & editing; **Paul Alex Wacoo**: Writing – original draft, Writing – review & editing.

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Data availability statement

This review did not involve the generation or analysis of any new data.

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