Salmonella and Salmonellosis in Public Health Implications

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Salmonella is one of the most important zoonotic pathogen agents, causing an estimated 93.8 million cases of gastroenteritis worldwide annually, with 155,000 deaths. Efforts to reduce transmission of Salmonella by food and other routes must be implemented on a global scale. Salmonellosis control strategies are based on two fundamental aspects: (a) the reduction of prevalence levels in animals and (b) protection against infection in humans.

Keywords: Salmonella ; salmonellosis ; animal health ; public health

1. Introduction

Salmonella spp. is recognized as a major zoonotic foodborne pathogen of economic significance in animals and humans; it causes an estimated 90 million cases of gastroenteritis worldwide annually, with approximately 155,000 deaths [1]. Even though salmonellosis is mostly reported as a foodborne disease, it has been estimated that about 10% of the cases are due to direct contact with animals [2].

Salmonella is a genus of highly diverse bacteria that live in the digestive tract of humans and animals. They are widespread in the environment thanks to their ability to survive and adapt even under extreme conditions [3].

Among the over 2600 *Salmonella* serovars described, clinical manifestations and mortality differ depending on both serovar and host characteristics (breed, age, sex, nutrition, and/or immunity) [4].

These serovars are divided into typhoidal and non-typhoidal serovars (NTSs); all of them can cause diseases in animals and/or humans with different levels of severity. Typhoidal serovars are highly adapted to the human host, which is their exclusive reservoir. They are, thserefore, only transmittable through human-to-human contact and cause a potentially life-threatening syndrome known as typhoid (*S. typhi*) or paratyphoid fever (*S. paratyphi*). Most European cases are considered imported cases and generally involve people returning from endemic countries [4].

NTSs are known as zoonotic agents. They are spread from animals and foods to humans but also through human-to-human close contact; they are widely present in the environment and can infect animals and contaminate both water and food. Usually, zoonotic salmonellosis occurs because of a true foodborne infection of animal or plant origin or through close contact with carrier animals [4].

2. An Update on Environmental Stresses Affecting *Salmonella* in Foods

The adaptation of *Salmonella* strains to different environmental stresses in foods has been widely reported, including known increased resistance to low pH, low water activity, and disinfectants, among others. Thus, *Salmonella* remains as an important concern in food processing environments, traditionally linked to the development of greater tolerance and cross-protection mechanisms, thus increasing the persistence along the food chain [5].

Besides the well-known effect of temperature, which is currently applied in pasteurized foods [6], recent studies have shown a growing interest in the acquired resistance mechanisms of *Salmonella* serovars against the presence of acids, low-water-activity foods, and biofilm formation on biotic or abiotic surfaces [7]. All these cumulative hurdles are applied at sub-lethal levels (especially in ready-to-eat foods), so that they promulgate an adaptative response and enable the survival of a larger fraction of *Salmonella* cells.

2.1. Acid Resistance of Salmonella in Foods

Acid adaptation allows *Salmonella* to withstand the challenges posed by low pH levels and potentially cause foodborne illnesses. *Salmonella* demonstrates the capacity to modify its physiological characteristics and regulate gene expression against exposure to low pH levels. This adaptation mechanism is especially interesting because of its viability in acidic foods, where conditions might inhibit the growth of other microorganisms [8]. In foodstuffs, weak organic acids like acetic, lactic, and citric acids can be present due to natural food constituents, fermentation processes, or intentional addition during food production to enhance preservation.

The optimum pH for *Salmonella* growth is generally known to be between 6.5 and 7.5, but the minimum pH value depends on many factors, such as the strain, the type of acid, or the synergistic action when combined with other stresses such as NaCl.

The increased tolerance to a low pH following acid habituation is referred to as the Acid Tolerance Response (ATR), which has been shown to be strain dependent [9]. This pH-dependent ATR might induce a posterior acid adaptation involving bacteria growth in mildly acidic conditions [10]. These investigations also shed light on the mechanisms of acid-induced cross-protection against ethanol stress in *S. enteritidis* during the growth phase [8], which may lead to more efficient mitigation strategies.

2.2. Survival of Salmonella in Low-Water-Activity Foods

The high frequency of *Salmonella* in low-water-activity (a_w) foods (such as powders, flours, dried fruits, spices, oily foods, and nuts) is a cause for concern. Recent studies have extensively reported on this situation due to the growing number of salmonellosis outbreaks related to these products [11]. These matrices comprise a wide range of the so-called Low-Moisture Foods (LMFs) as being those with reduced water content, making them less favorable for the growth of most microorganisms. According to Food and Drug Administration (FDA) standards, they have an a_w at 25 °C of less than 0.85 [12]. These conditions do not allow bacterial growth; however, several studies have demonstrated the survival ability of *Salmonella* spp. in different LMFs [13][14] for months or even years, thus potentially causing adverse health effects for susceptible population groups. Microbial contamination can occur when handling and/or processing any contaminated LMF and/or from environmental contamination, suspended air particles, or inert surfaces [15]. Adaptive responses in *Salmonella* help it survive by accumulating compatible solutes, including proline, glycine, betaine, ectoine, and trehalose, leading to reduced water loss [16]. Furthermore, osmoregulation plays a vital role in maintaining the turgor pressure of the bacteria through increasing the intracellular concentration of compatible solutes [17][18].

Importantly, the use of cocktails may ensure that novel processes can remove the most resistant strains, as reported in previous studies [19][20]. Some of the latest studies deal with the relationship between moisture content, as a better indicator than temperature, and a_w in the thermal inactivation of *Salmonella* in LMFs [21], the effect of food structure combined with emerging technologies [22], and the design of novel test cells to better estimate a_w in the thermal resistance of *Salmonella* strains [23].

2.3. The Biofilm Formation of Salmonella in Food-Processing Environments

The different survival mechanisms of *Salmonella*, such as the formation of biofilms, are hypothesized as possible factors for the onset of foodborne diseases. There is clear evidence of the formation of biofilms by *Salmonella* in foods and in different materials present in food processing environments [24][25][26]. *Salmonella* produces a biofilm matrix that is mainly composed of fimbriae (curli) and cellulose [27]. The ability of *Salmonella* to adhere and form biofilms is influenced by multiple factors, such as the composition of the growth medium, the developmental stage of the cells, the characteristics of the inert material, the contact time, the presence of organic substances, and environmental conditions like temperature and pH [28].

Control strategies against *Salmonella* and microbial biofilms overall have been traditionally based on the use of chemical disinfectants, widely applied in the meat industry [29]. However, their effectiveness may differ depending on the type of surface. Other drawbacks such as the increased bacterial resistance to sub-lethal concentrations of disinfectants and the presence of chemical residues preclude their use as a valid antibiofilm strategy. Antimicrobial resistance and toxicity issues have been associated with the use of antibiotics or nanoparticles. Other control strategies still require the application mode and targeted dose to be optimized, as the use of enzymes and quorum-sensing inhibitors are of dubious efficacy against relevant biofilms [30]. Among the physical treatments, pulsed light and UV-C radiation could inactivate the formation of *Salmonella* biofilms [31].

Recent developments in biofilm eradication are based on biocontrol strategies such as the use of bacteriophages. Ashrafudoulla et al. [32] evaluated specific lytic bacteriophages against *S. thompson* biofilms on eggshells, which showed better efficacy when using bacteriophage cocktails. In contrast, temperate *Salmonella* bacteriophages can confer greater virulence and resistance to adverse factors, as shown by *S. typhimurium* biofilms. Therefore, the expression of virulence genes and metabolic pathways of *Salmonella* induced by the presence of bacteriophages deserves to be studied further [33].

2.4. Predictive Microbiology Models for Estimation of the Microbial Behavior of Salmonella in Foods

Since *Salmonella* can be present in several food commodities, microbial behavior along the food chain has been extensively studied over recent decades. Predictive microbiology is a field that involves using mathematical models and statistical tools to predict the behavior of microorganisms in various environments [34]. Predictive models aim to describe the effect of a certain process (e.g., disinfection, heat treatment, storage, etc.) modulated by a range of environmental factors (e.g., pH, temperature, a_w, etc.) on the microbial population of interest. Predictions can be quantified through different parameters describing microbial growth, survival, or inactivation, such as maximum growth rate, lag phase, inactivation rate, etc. [35]. As such, applications of predictive microbiology may be oriented to different areas, including food innovation, process control, risk management, reduction of food wastage, design of experiments, and training. There is a wide range of predictive models for describing *Salmonella* behavior in various food categories. Growth, survival, or inactivation ability has been extensively explored in eggs and egg products [36][37][38], meat products [39][40][41], melons [42][43][44], low-moisture foods [45][46][47][48][49], and leafy vegetables [50][51], among others.

While the effect of the most representative environmental factors, such as temperature, pH, and water activity, on *Salmonella* behavior has been properly characterized by the use of dedicated models, research efforts are focused on the effect of emerging preservation technologies or novel antimicrobial agents, as shown in some recent papers. Shahdadi et al. [52] conducted a systematic review and modelling of the role of bacteriophages against *Salmonella* in meat products, while Austrich-Comas et al. [53] evaluated a combined strategy using starter cultures, storage, and high-pressure processing in dry fermented chicken sausages. The use of radio frequency as an inactivation technology against *Salmonella* in treated eggs was successfully modelled by Bermúdez-Aguirre and Niemira [54]. Other models for *Salmonella* using pulsed ohmic heating, UV-radiation, ultrasound, and microwave technologies were reviewed by Alvarenga et al. [55]. It is clear that predictive models can aid in decision making to establish standards for processing by using emerging technologies. Future work should be oriented toward incorporating specific parameters that accurately quantify the effectiveness of emerging technologies in food preservation.

For industrial and health authorities, the use of web interfaces is becoming crucial for a more effective interpretation of predictive models. MicroHibro software (www.microhibro.com, accessed on 15 August 2023) [56] was developed by the University of Córdoba and includes a range of freely available applications related to predictive modelling (safety and shelf life), sampling plans, and risk assessment tools [57]. Currently, MicroHibro software is being updated to include quality or shelf-life models and more advanced risk assessment features.

3. Antimicrobial Resistance

3.1. Salmonella and Antimicrobial Resistance: Preface

Several factors of bacterial chromosomes or plasmids may be the cause of *Salmonella* antibiotic resistance [58][59]. These genetic determinants might be in charge of expressing the intrinsic resistance mechanisms linked to the synthesis of beta-lactam antibiotics, alterations in the composition of antimicrobials caused by bacterial enzymes, differences in the permeability of bacteria, the existence of efflux pumps, or changes in target receptors.

The expression of acquired resistance mechanisms, which arise from point mutations in chromosomal genes (e.g., monophasic strains of *S. typhimurium*) or the acquisition of mobile elements like plasmids, transposons, or genomic islands can also result in antimicrobial resistance (AMR) [59]. Resistance transmission can happen vertically between different bacteria or horizontally within the same species or genus.

A variety of reasons, including improper use of antibiotics in human and veterinary medicine, unhygienic environments and practices in healthcare settings, and pathogens that are resistant to treatment spreading via the food chain, can lead to the development of resistance. Antimicrobials become less effective over time and eventually worthless as a result of this [60]. The primary selective pressure resulting from antibiotic overuse and abuse is still thought to be responsible for the appearance, selection, and spread of microorganisms resistant to antibiotics [61]. Gut bacteria can develop resistance to certain antibiotic substances, which they can then vertically transfer to *Salmonellae* sharing the same ecological niche.

One of the main causes of global concern for health authorities has been the increase in cases of gastroenteritis and sepsis linked to *Salmonella* strains that are becoming more resistant or even multi-resistant to conventional antimicrobials (e.g., beta-lactams, aminoglycosides, and quinolones, among others). These strains include mainly the Typhimurium serovar and its monophasic variants (mST) [62][63][64] as well as *S. infantis* and *S. kentucky* [65]. Consequentially, resistant infections are on the rise, causing therapeutic failures and longer hospital stays and thus heavily affecting public health and the economy. With over 90,000 salmonellosis cases reported every year in the EU, the EFSA has estimated that the overall economic burden of human salmonellosis could be as high as EUR 3 billion per year (https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/factsheetsalmonella.pdf, accessed on 28 June 2023).

3.2. Key Findings

The annual collection of data on Antimicrobial Resistance (AMR) pertaining to zoonotic and indicator bacteria from humans, animals, and food sources is a collaborative effort undertaken by Member States (MSs) and reporting countries. The resultant datasets are jointly analyzed by the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) and are published in an annual EU Summary Report. The most recent report provides an overview of the key findings of the period from the harmonized AMR monitoring conducted between 2020 and 2021, with a specific focus on *Salmonella* spp. in humans and food-producing animals, including broilers, laying hens and turkeys, fattening pigs, and cattle under 1 year of age along with the associated meat products [66].

Among the reporting countries, the number of *Salmonella* spp. in isolates from human cases varied considerably. Of the 26 reporting countries, including those within the EU and EAA countries, six countries reported very few (<100) human isolates, while three countries reported more than 1000 isolates.

Over the period 2013–2021, declining trends in resistance to ampicillin and tetracyclines in isolates from humans was observed in 13 and 11 countries, respectively, coinciding with a decrease in the prevalence of *S. typhimurium*, a serotype commonly associated with pigs and calves. From data reported in 2021, the resistance to fluoroquinolones, specifically ciprofloxacin, was moderate in *Salmonella* isolates from fattening pigs (10.1%) and cattle under 1 year of age (calves) (12.7%). In contrast, in 2020, resistance to ciprofloxacin was noticeably high in isolates recovered from broilers (57.5%), fattening turkeys (65.0%), broiler carcasses (69.3%), and turkey carcasses (46.9%). In 2021, *Salmonella* isolates from humans displayed an average rate of 14.9%, with the lowest levels observed in *S. typhimurium* (7.6%) and *S. typhimurium* monophasic variant (8.9%) and high to extremely high levels in *S. infantis* (33.9%) and *S. kentucky* (78.1%).

It is noteworthy that approximately 95% of isolated *S. infantis* serovars identified in the EU were traced back to broilers and their derived products [65]. Recent research has demonstrated a strong association between the *S. infantis* serovar and elevated antimicrobial and multidrug resistance, resistance to disinfectants, increased tolerance to environmental mercury, heightened virulence, and an enhanced ability to form biofilms and attach to host cells [65].

Resistance to third-generation cephalosporins remained notably low in isolates from humans in 2021 (1.1% to ceftazidime and 1.1% to cefotaxime, on average) and was seldom detected in isolates from animal and carcass origins in 2020–2021, except for calves (2.6% to cefotaxime and 1.3% to ceftazidime) and broiler flocks (2.1% to cefotaxime and 2.0% to ceftazidime). Conversely, combined resistance to fluoroquinolones and cephalosporins was very low in isolates from both humans and animals but exhibited higher prevalence in certain *Salmonella* serovars (e.g., *S. kentucky* and *S. infantis*) [4].

4. Control Strategies in Animal Health

4.1. Feeding Strategies

In the case of the poultry and pig industry, the main reservoirs of *Salmonella*, feeding strategies aimed at optimizing intestinal functions may have an impact on the colonization of *Salmonella* in the digestive tract. Among them, it must highlight the acidification of feed by means of organic acids, the use of probiotics, prebiotics, or phytobiotics, and the new lines of research on the incorporation of essential oils (EOs) extracted from plants [67][68]. Most of these products are used in animal health as feed additives, and their approval as therapeutics requires proven scientific studies that demonstrate their antimicrobial efficacy, effect on animal production, and safety for public and environmental health.

The efficacy of EOs obtained mainly from oregano, cinnamon, thyme, and citrus fruits have been evaluated against *Salmonella* serovars [69][70][71]. As an example, the effect of EOs against *Salmonella* serovars isolated from human outbreaks and river water has recently been investigated [68]. This research showed that oregano best inhibited the growth of clinical and environmental Saintpaul, Oranienburg, and Infantis serovars, followed by thyme and grapefruit EOs. The antimicrobial property of the oregano EO, higher than even antibiotic ampicillin, may be attributed to the terpenoids thymol and carvacrol. Therefore, this study concludes that the use of oregano and thyme EOs in conjunction with other oils or bactericidal agents may enhance their effectiveness against infections caused by atypical *Salmonella*.

In addition, different authors have continued their research on assessing the combined effect of these natural substances with traditional antimicrobials (AMBs) as an effective option to reduce bacterial resistance and administration doses [72][73]. In this sense, the synergistic effect between EOs with the main AMBs used against *Salmonella* (enrofloxacin, ceftiofur, and trimethoprim-sulfamethoxazole) has been reported, highlighting the higher percentage of total synergies of trimethoprim-sulfamethoxazole with four EOs (cinnamon, clove, oregano, and red thyme), the most effective combination being enrofloxacin and cinnamon EO [67][73]. These results support the need to expand these trials to more clinical strains and to investigate the mechanisms of action of these synergies.

4.2. Non-Feeding Strategies

4.2.1. Bacteriophages or Phages

Bacteriophages or phages are viruses that infect and replicate in bacteria until they lyse. They have a capsule and genetic material like eukaryotic viruses. They are natural bactericides and probably one of the most widely distributed microorganisms in the biosphere. Despite their potential usefulness in the treatment of infections, the study of their feasibility has been relegated to the use of antibiotics. In the current context, with the reduction and/or withdrawal of antibiotics from the medical-veterinary scene, alternatives such as phages or bacteriophages may be useful for the treatment and control of bacterial infections such as *Salmonella* [3].

When it comes to prophylaxis, animal therapy, and reducing the number of bacteria in animal-based food products, bacteriophages are thought to be a valuable alternative to antibiotics [74]. Their host-specificity makes them natural, non-toxic, and feasible for therapeutic application, allowing them to attack only the targeted bacteria while safeguarding the rest of the microbiota. Since the immune system can tolerate phages well, they also have the advantage of preventing host allergies [75].

Phage-based methods of controlling *Salmonella* have been tested in poultry [76][77][78][79] and, to a considerably lesser extent, in pigs [80]. In fact, the environment found in chicken farms may be a valuable source of *Salmonella* phages. It has been found that broiler chicken farms in Spain have more diversified *Salmonella* bacteriophages than layer ones based on the most common serovars [77]. However, more research is required to understand the epidemiology of phages in relation to other serovars.

Furthermore, some researchers have recently investigated the use of microencapsulated bacteriophages incorporated into feed for *Salmonella* control in poultry [78][79]. In a first study, in vitro and in vivo gastrointestinal survival of non-encapsulated and microencapsulated *Salmonella* bacteriophages and its implications for bacteriophage therapy in poultry were reported. Significant differences were observed in the results between the phage delivery of in vitro studies compared with in vivo studies [78].

4.2.2. Vaccines

Strategies based on vaccination for the control of *Salmonella* spp. have proven to be a very effective tool for controlling salmonellosis in species such as poultry. For that reason, the manufacturing of vaccines for the poultry industry is based on strains of *S. enteritidis* and *S. typhimurium* [81].

On the contrary, in swine there are currently no effective commercial vaccines. The main problem with medical prophylaxis against *Salmonella* in swine is that there is no cross-immunity between the different serovars (e.g., Typhimurium, Rissen, Derby, Anatum, Bredeney, etc.); therefore, it would be necessary to use specific vaccines (autologous or autovaccines) against the serotype involved in the infection/disease on the farm or to design vaccine candidates that included the predominant serotypes in the geographical area and/or farms involved [3].

The different types of vaccines available on the market are live-attenuated, inactivated, and subunit vaccines [82]. The protection conferred by live vaccines is theoretically greater since they promote a cellular-based response, which *a priori* is ideal for facultative intracellular pathogens such as *Salmonella*. In addition, if they are administered orally, they will manage to produce immunoglobulin-A in the intestine, the main component of the immune system in the control of digestive pathogens. However, these vaccines have certain disadvantages, such as the need to withdraw any antibiotic treatment during oral administration of the vaccine, their cost, and the potential risk of reversion to virulence and biosafety [3].

4.2.3. Biosecurity

Biosecurity is the most effective and inexpensive disease control measure, aimed at managing the risks posed by diseases to the economy, environment, and human health [83]. The application of biosecurity measures to reduce the levels of prevalence of infections/diseases, with special attention to those that pose a risk to public health (e.g., salmonellosis), should be one of the main objectives of health authorities [84].

The application of strict hygiene and biosecurity measures not only improves the situation of farms with respect to specific pathogens but also improves the overall health of farms. In the specific case of *Salmonella* spp., in intensively reared white pigs and in intensive poultry farming, numerous biosafety protocols and practical guides have been described both at the farm and slaughterhouse level. The most critical points are related to cleaning and disinfection protocols [3].

Salmonella Cleaning and Disinfection Protocols

The objective of sanitation is to clean and disinfect equipment and materials that enter or remain on farms, including the personal hygiene of farm staff. Following the sanitation program guidelines helps to exclude the presence of pathogens on the farms before they can be spread [84]. As an example, the efficacy of disinfectant misting in the lairage of a pig abattoir to reduce *Salmonella* in pigs prior to slaughter has been reported [85]. This comprises the following: (1) application of high-pressure water to remove organic matter; (2) use of detergent with rinse (e.g., sodium hydroxide or hypochlorite); (3) use of disinfectant without rinsing (e.g., chlorocresol or quaternary ammonium); (4) drying for at least 24–48 h; and (5) fumigation based on cypermethrin.

5. Conclusions

Efforts to reduce the transmission of *Salmonella* through food and other routes must be implemented using a One Health approach. The control of salmonellosis is based on two fundamental aspects: the reduction of prevalence levels in animals and the protection of humans from infection.

At the food chain level, the prevention of salmonellosis requires a comprehensive approach at farm, manufacturing, distribution, and consumer levels. Food operators and health authorities play a crucial role in preventing *Salmonella* transmission to consumers by ensuring safe food handling, monitoring and enforcing hygiene standards, and swiftly responding to foodborne outbreaks. Their collaboration safeguards public health and reduces the risk of foodborne illness, underscoring the importance of their roles in safeguarding food safety.

A significant concern is the rise of *Salmonella* MDR strains, which are responsible for foodborne illnesses that are common throughout the world. In fact, multidrug resistance (MDR) complicates the use of antibiotics to treat infections, raises healthcare expenses, lengthens hospital stays, and increases mortality.

Finally, several environmental and management factors have been associated with high levels of *Salmonella* spp. in the animal population. Based on these risk factors, different prevention and control methods related to hygiene and management, health and biosafety, animal welfare, and feeding strategies have been proposed.

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