Chapter

Biocide Use for the Control of Non-Typhoidal *Salmonella* in the Food-Producing Animal Scenario: A Primary Food Production to Fork Perspective

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Abstract

Biocides are a group of substances commonly used in food production settings to destroy or control a wide range of microorganisms, which can be present in food of animal origin, since contamination can occur in the several steps of the food production chains. In order to achieve the desired results, the users of biocides must first understand the diverse characteristics of such compounds, mainly the usage requirements, limitations, and the factors affecting the activity of biocides. Food-producing animals and their products, namely meat and eggs, represent a major source of non-typhoidal *Salmonella* for humans and are associated with foodborne outbreaks worldwide. The prevention of cross-contamination, which can occur in any step of the food production chain, is essential for the ultimate objective of producing safe food products. The correct use of biocides, along with good hygiene and manufacturing practices, is one of the pillars of *Salmonella* spp. control and should be implemented in all steps of the food production chain. The present chapter reviews the accumulated knowledge on the use of biocides to control non-typhoidal *Salmonella*, from a farm to fork standpoint, along with the possible impacts on human health arising from improper use.

Keywords: biocides, non-typhoidal *Salmonella*, control, farm to fork, food safety, food production chain

1. Introduction

Biocides, from a broad point of view, are substances with the ability of killing living organisms, meaning that this is an all-embracing group, which includes numerous active substances with different targets, ranging from animals, plants, to microorganisms. The use of biocides specifically targeting microorganisms is widely spread in modern societies, mainly due to an increased alarm regarding microbial environmental contamination of living spaces [1]. Regardless of the growing usage of such biocides, antimicrobial chemical substances have long been regarded as very useful for mankind, for medical, agricultural, and food safety purposes [2]. Unlike antibiotics, which are used to treat infections in humans and animals since they are suitable to be in contact with living tissues, antimicrobial biocides are applied on contaminated suspensions or surfaces reducing the numbers or eliminating microorganisms [1]. These substances are available in very diverse formulations and used not only at an industrial level, but also at the households of consumers, for multiple sanitation procedures. Likewise, these biocidal substances are also used to control the dissemination of microbial pathogens among animal populations and to prevent the leakage of such pathogens from farms [2]. The selection of the most appropriate antimicrobial biocide for a specific application is highly dependent on multiple factors, which can seriously affect its effectiveness [3]. Even with the growing concern regarding the possible effects of such a vast use of these substances in various sectors, antimicrobial biocides are considered to be indispensable for food safety assurance, as their use is imperative along the food production chains, from livestock production up to food industries and retailers [4].

Non-typhoidal *Salmonella* (NTS) is one of the most notorious and studied foodborne pathogens worldwide due to its impact on human health, with an estimated burden of 93.8 million cases of disease and 155.00 deaths per year globally, affecting populations of both developing and developed countries [5]. In humans, NTS infection cases are commonly restricted to a self-limiting gastroenteritis, characterized by nausea, vomiting, and diarrhea starting within a 6–48 hours interval after exposure; however, life-threatening complications can arise from the initial gastrointestinal tract infection in more susceptible groups, such as infants or immunosuppressed and HIV-positive individuals, among others [6, 7]. Despite not being considered necessary for uncomplicated human infections, empirical antimicrobial therapy should be considered in patients belonging to the increased risk groups and recommended whenever bloody diarrhea is present [8]. The upsurge of antimicrobial resistant NTS isolates seen over the past decades is therefore worrying, and this phenomenon has long been identified as a serious global public health concern [9]. As mentioned, NTS is generally considered to be a foodborne pathogen, though human infection cases can occur without the ingestion of contaminated food [6]. Nevertheless, the epidemiological role of food in NTS outbreaks is strikingly greater when comparing with other sources of infection, as direct animal contact or with animal environments [10, 11]. Additionally, food of animal origin has been largely implicated in NTS foodborne outbreaks when comparing with produce [12–14]. The major food vehicles of animal origin associated with outbreaks over the years have been eggs, poultry meat, pork, and to lesser extent, beef and dairy products [15]. Previous works have highlighted the public health impact of eggs [16], poultry and poultry meat [17], and pork [18, 19] in the salmonellosis scenario. There are several steps along the food production chains in which NTS can unintentionally taint food; therefore, complex strategies to avoid the presence of this foodborne pathogen in the final product must be adopted.

This chapter aims to provide a straightforward review of the most relevant available information regarding the use of antimicrobial biocides for the control of non-typhoidal *Salmonella* in the multiple points of the animal-origin food chains, and its possible implications, with a farm to fork perspective. A brief description concerning antimicrobial biocides and their main characteristics will be presented. Additionally, information regarding non-typhoidal *Salmonella* and its dissemination along the food chains will be reviewed. Finally, the use of biocides to control non-typhoidal *Salmonella*, biocide resistance, and possible implications of biocide usage will be discussed.

2. Biocides

Generally, a biocide can be defined as an active substance, or a formulation containing at least one active substance, used with the intention of destroying or controlling the effect of any harmful organism to human or animal health by any means other than mere physical or mechanical action [20]. Since the term biocide encompasses a wide spectrum of substances with diverse applications, in the scientific literature it is common to be replaced by disinfectant or sanitizer when addressing chemical substances with antimicrobial activity, in part due to different classifications and legislations. Within the scope of this chapter, only biocides used mainly for disinfection purposes will be addressed.

The legislation and the agencies that regulate these chemical substances have suffered changes over passed decades, mainly in the European Union (EU) and in the United States of America (USA). According to the EU's legislation, biocides are divided in four main groups regarding their purpose: disinfectants, preservatives, pest control products, and other biocidal products [20]. The EU's Biocidal products regulation (Regulation (EU) No 528/2012) further divides biocides used for disinfection in five groups: human hygiene biocidal products, private area and public health area disinfectants, veterinary hygiene biocidal products, food and feed area disinfectants, and drinking water disinfectants.

A different classification is seen in the USA as biocides with antimicrobial activity are classified as public health antimicrobial pesticides and are under the authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Within the US legislation, these antimicrobial pesticides are classified according to the degree of effectiveness as sterilants, disinfectants, and sanitizers. While sterilants destroy all forms of bacteria and fungi, including their spores, and even viruses, disinfectants destroy or irreversibly inactivate bacteria, fungi, and/or viruses but not their spores. Disinfectants are subdivided based on their efficacy as hospital, general or broad-spectrum, and limited disinfectants. With the lowest efficacy of all the public health antimicrobial pesticides, sanitizers reduce, without necessarily eliminating microorganisms from inanimate environment, and are divided as non-food-contact sanitizers and food-contact sanitizers [21].

2.1 Antimicrobial biocides

In terms of disinfection purposes, there are several biocidal active substances deriving from different chemical categories [22]. Overall, disinfectants can basically be divided into two groups, the oxidizing and the nonoxidizing. Among oxidizing disinfectants are halogens such as chlorine, chlorine dioxide, iodine, and peroxides, mostly peracetic acid and hydrogen peroxide. Within the group of nonoxidizing disinfectants are quaternary ammonium compounds (QAC), amphoterics, aldehydes, phenolic compounds, biguanides, and acid anionic agents [23, 24]. Their activity, and ultimately the desired effect, can be influenced by different factors, mainly the initial concentration, length of time of contact, temperature, pH, the presence of organic matter, and the type of surface [25–27]. Together with external factors, the nature of the microorganisms, their number, location, and condition, namely the presence of a biofilm, can also have an impact on the activity of biocides [27, 28]. When these factors are not considered, ineffective disinfection procedures are likely to occur [29]. The typical usage of antimicrobial biocides, the factors affecting their activity, their advantages and disadvantages have been summarized by different authors in previously published reviews [3, 29, 30].

The mechanisms of action of biocides are not fully understood, but generally they can be divided according to the cell structures in the bacterial cells where the interactions occur to produce an antimicrobial effect, specifically the outer cell components, the cytoplasmic membrane, or the cytoplasmic components [31]. In order to develop their antimicrobial activity, the biocidal substance must be transported to the bacterial cell surface, adsorb, diffuse, penetrate, and interact with its target, and all of these processes are time-dependent [32]. In fact, after biocide exposure, the bacterium expresses multiple mechanisms to reduce the amounts of biocidal substance and to repair damages. Consequently, if the exposure is short, the stress and damage induced by the biocide are reversible, but long exposures lead to cell death due to irreversible changes in membrane integrity, leakage of cytoplasmic constituents, and coagulation of intracellular materials [2].

Despite being used for the same reasons and aiming for similar outcomes, some of the characteristics of the biocides used in animal production settings are different when comparing to the ones used in food processing environments. Biocides used for disinfection of animal houses are usually strong, and on some occasions, such as contaminated surfaces, toxic biocidal chemicals are used; in contrast, biocides used in food processing premises are commonly of low toxicity and applied in higher dilutions [26].

Though precise information regarding the actual biocidal substances being used on farms is not readily available since there are several commercially available disinfectant formulations, among the most common are hydrogen peroxide, acetic acid, QACs, aldehydes such as glutaraldehyde, formaldehyde, and isopropanol [33]. In the food industry, the biocidal substances used in commercially available formulations include amphoteric surfactants, polymeric biguanides, QACs, chlorhexidine, chlorine and chlorine-based derivatives, acid anionic agents, hydrogen peroxide, and peracetic acid since these biocidal groups are suitable to be used on food-contact surfaces [4, 32].

These substances or products are extremely important and broadly used for cleaning and disinfection (C&D) procedures of surfaces and environments in the multiple steps of the food production chain, from farms to abattoirs and food processing and handling establishments and even at the households of consumers [30, 34]. As previously mentioned, NTS is a major foodborne illness hazard, thus controlling its movement and persistence across the food production chains is imperative to diminish its impact on human health.

3. Non-typhoidal *Salmonella*

Despite belonging to the same species (i.e., *Salmonella enterica*), non-typhoidal and typhoidal *Salmonella* serotypes have very distinct behaviors regarding the hosts. While typhoidal *Salmonella* serotypes, specifically Typhi and Paratyphi, are highly adapted to the human host, NTS serotypes can infect a broad range of hosts, including humans, though some NTS serotypes are also known to be species restricted [35]. This level of adaptation of each serotype to specific hosts has clinical, epidemiological, and public health impacts, since the degree of pathogenicity of the same serotype can vary among different hosts. As previously mentioned, *Salmonella* Typhi and Paratyphi, which are highly adapted serotypes to humans and are the etiological agents of typhoid and paratyphoid fevers, respectively, are not considered to be pathogenic to other animals. A similar scenario is observed regarding serotypes highly adapted to animal hosts, namely *Salmonella* Gallinarum responsible for fowl typhoid, which is not considered to be pathogenic to humans. On the other hand, ubiquitous or generalist serotypes, such as *Salmonella* Enteritidis or Typhimurium, can affect a broad range of hosts, including humans [36] and are among the most frequently implicated in NTS-associated foodborne illness cases [37, 38]. It is assumed that infections with generalist serotypes are mainly characterized by gastrointestinal manifestations, with high morbidity but with low mortality, and that diseases arising from host-restricted serotypes have low morbidity and high mortality [39]. Nevertheless, some exceptions to this host adaption/pathogenicity degree association are known to occur, for example, *Salmonella* Choleraesuis and Dublin, two serotypes that have as primary hosts pigs and cattle, respectively, which are also responsible for systemic disease in humans [36]. Within the scope of the present chapter, the use of NTS will be replaced simply by *Salmonella*.

3.1 Food production chains and *Salmonella*

The food production chains have evolved greatly since the past century. The world's most industrialized countries have seen a paradigm change on how food is produced, shifting from small-sized farms supplying local markets to international networks producing and supplying food to large amounts of consumers, though it is estimated that 50–70% of the global food is still produced by smallholder farmers [40]. With a projected world population of almost 10 billion by 2050, and an expected growth of the income in low and middle-income countries, a higher consumption of meat, fruits, and vegetables is foreseen, resulting in additional efforts in the production chains and on natural resources [41]. These circumstances highlight the global challenge of producing enough food to satisfy the needs of the world's growing population, but in order to do so, food safety systems will also have to adapt to the changing needs of both developed and developing countries, enabling global food security [42].

Many stakeholders take part in the food of animal-origin production chains, ranging from cereal producers, feed mills, animal farms, transport operators, abattoirs to food processing industries. These networks of stakeholders can be extremely intricate and highly dependent of international trade, with globalization having a very important role. Feed ingredients can, in some cases, originate from different continents, traveling long distances before being processed in feed mills. The role of feed as a source of *Salmonella* for animals and humans is well known, and all efforts should be made to avoid feed contamination. In the first place, it involves preventing the entry of *Salmonella* in the feed mill's facilities by obtaining uncontaminated feed ingredients and managing several other factors, including flow of personnel and the control of unwanted animals (rodents and wild birds), among others [43].

When comparing different animal species, namely poultry and pigs, some variations in the production cycles are found, with a stratified organization of animal farms, such as breeder, multiplier and finishing or fattening farms, and as such live animal transport is necessary within and between countries. In fact, one of the main challenges regarding the control of *Salmonella* is the prevalence levels among animal populations. In Europe, several countries have implemented strict *Salmonella* surveillance and control programs for poultry (broilers, turkeys, and laying hens) [44–46] and, to a lesser extent, for pigs [47] and cattle [48–51]. Generally, these programs rely on the collection of samples for *Salmonella* detection and on the implementation of restrictions on farms whenever positive results are found. Additionally, a big emphasis is put on the application of biosecurity measures in farms as an effort to avoid the entry of *Salmonella*. Some of the most relevant biosecurity measures are associated with correct cleaning and disinfection (C&D) procedures of the houses where animals are reared in and of the transport vehicles [52, 53]. Moreover, each step of the life cycle of a food-producing animal (birth, rearing, slaughtering) can take place in a different region of the same country or even in different countries.

Finally, before being available to consumers, food-animal products must be carried to food processing facilities and/or to retailers where cross-contamination can occur. As reviewed by Carrasco et al. (2012), there are multiple scenarios where *Salmonella* can contaminate food through food handlers, food-contact surfaces, equipment, and utensils emphasizing the importance of preventive control measures, namely adequate sanitation procedures in food processing and handling facilities but also the consumer's knowledge on good hygiene practices [54].

There has been an increase of the number of food business operators adopting the vertical integration structure, connecting its upstream suppliers with the downstream buyers. The ultimate goal of integrative growth is to increase the business profitability by controlling the most important related activities [55]. Vertical integration is also considered to be a part of the food business operator's private control strategies to tackle food safety hazards along with Hazard Analysis and Critical Control Point (HACCP) systems and third-party certifications [56]. On the other hand, non-integrated food business operators are more likely to be affected by both upstream and downstream operators, not only regarding safety issues but also economically since they are more dependent.

The poultry industry, specifically the broiler sector, was the first to adopt a vertically integrated organization after World War II, during the 1950s, in the USA. Vertical integration of the pig sector was only achieved much later, due to technical and husbandry issues [57]. Nevertheless, at the present time these are the two main animal species reared by large vertically integrated food business operators, especially in high income countries.

Eggs, poultry meat, and pork are the main sources of human salmonellosis cases through contaminated food, and as such, stronger efforts to control *Salmonella* must be put in place along the poultry and pig-associated food production chains, namely the correct use of antimicrobial biocides.

4. Biocide use throughout the food production chain

To control the spread of *Salmonella* along the food production chain, several measures must be put in place at different stages starting at feed mills to assure high food safety standards. An efficient control of *Salmonella* in feed mills is based on blocking the entry of this pathogen firstly, reducing the chances of *Salmonella* multiplication within the facilities, and by rendering the final product *Salmonella*-free by using thermal process or adding chemicals to feed [43].

Despite the low-moisture environment found in feed mill facilities, which impairs bacterial multiplication, *Salmonella* persistence in such circumstances is known to occur, and it is associated with biofilm-forming capability [58]. In these situations, chemical disinfection is necessary to eliminate this source of feed contamination. Despite being a crucial step of the C&D procedure, it seems that physical cleaning can also contribute for the dissemination of the bacterial contamination within the mill facilities [59].

The use of disinfectant formulations combining aldehydes, namely formaldehyde and glutaraldehyde and QACs, applied at high concentrations has been pointed out as the most appropriate against *Salmonella* on surfaces that are not easily cleaned [60]. A direct application of a 30% formaldehyde commercial solution is able to reduce *Salmonella* contamination down to undetectable levels in different types of surfaces, including stainless steel, plastic, polypropylene haul bags, rubber belts, and rubber tires [61]. However, a 70% ethanol-based disinfectant (P3- AlcoDes) and a peroxygen-based disinfectant (Virkon S) were reported to be the most effective when used on surfaces outperforming other disinfectants, even those with a QAC-aldehyde formulation, under laboratory conditions [62].

The specificities of feed mills must be considered by the business operators when choosing the biocidal formulations to be used for disinfection, specifically the need to maintain low levels of moisture. Once detected, *Salmonella* contaminations must be dealt with as soon as possible and rigorous monitoring after C&D should provide information regarding the effectiveness of the procedure. When comparing the legislation of different countries, the responsibility is placed upon the business operators as they must assure the production of safe compound feed. Besides, the economic costs of implementing controls to obtain *Salmonella*-free feed are considered to be limited and that the prevention of dissemination of this pathogen to animals through feed is economically achievable, supporting the implementation of *Salmonella*-negative regulation [63].

The environments of the houses/farms where animals are raised in pose serious challenges when considering C&D procedures, mostly due to the amount of organic matter, construction materials used, and multiple fixtures. To obtain the best results possible, all animals should be moved out of the areas or houses before C&D can be started and new animals should only be moved in after C&D has been completed, a system commonly referred to as all in/all out.

There are multiple reports on the efficacy of C&D procedures for *Salmonella* control in poultry farms based on the application of different biocides, either from broiler [64–69], laying hen [70–73], or duck farms [74]. The most frequently used disinfectants were phenol-based, namely formaldehyde, glutaraldehyde, and QACs. Though the use of such substances is considered to result in effective C&D, the application of glutaraldehyde, formaldehyde, and peroxygen solutions at a concentration of 1% was unable to eliminate *Salmonella from a poultry house under experimental conditions* [75]. Wall and floor crevices, drinkers, feeders, and vents can be problematic since these areas/fixtures can promote bacterial persistence, mainly due to the accumulation of dust or organic matter protecting bacteria from the action of biocides [68, 69]. Incomplete disinfection of the houses or of the equipment, leading to *Salmonella* persistence, is likely to promote early *Salmonella* exposure to new laying hen flocks [71] and is considered to be one of the risk factors for the *Salmonella* status of broiler flocks at the end of the production cycle [67].

There are different types of disinfectant formulations, based on QACs, aldehydes, peroxygen or peracetic acid-based, iodine-based compounds or chlorocresols are available to be used on pig holdings for *Salmonella* control, though with diverse effectiveness levels [76]. Disinfectants based on sodium hypochlorite or QACs are believed to be able to eliminate *Salmonella* from pig houses when properly applied after a correct cleaning step [77]. Additionally, in pig housing settings, it seems that better results are achieved using concentrated phenolic disinfectants rather than peroxygen-based products [78]. Even though formulations using combinations of glutaraldehyde and QACs are more effective than iodine-based disinfectants, over-dilution of glutaraldehyde-QACs disinfectants affects its performance, leading to procedure failure and to *Salmonella* persistence in pig houses after C&D [76]. In pigs, as well as in poultry, the maintenance of *Salmonella* on the environment hinders the effects of all other biosecurity measures, such as feed or rodent control. The environment can be contaminated even though it looks clean or undergoes multiple C&D routines, contributing greatly for the transmission of *Salmonella* within pig farms [79].

Abattoirs are a paramount step for *Salmonella* cross-contamination control. Apparently healthy animals can be *Salmonella* carriers, which can easily contaminate the abattoir's facilities and/or equipment, transferring *Salmonella* to, or even infecting negative animals in the lairage area or transferring the pathogen to carcasses during the slaughtering processes. Due to the likely event of environment contamination, highly effective C&D procedures must be adopted. Disinfection in abattoirs can be carried out using one or more of the many formulations suitable to be used in the food industry premises including alcohols, chlorine-based compounds, QACs, oxidizing agents, persulfates, surfactants, and iodophors [80]. As an additional effort to reduce to possibility of cross-contamination, logistic slaughter should be implemented whenever the *Salmonella* status of the animals is known, meaning that *Salmonella*-positive animals should only be slaughtered after negative animals. The effectiveness of this measure is strictly dependent of the absence of *Salmonella* from the environment and equipment of the abattoir [81].

In pig slaughterhouses, it has been shown that a main source of carcass contamination is the lairage environment rather than the gut or the lymph nodes of the slaughtered animals [82]. When comparing different protocols for *Salmonella* elimination in lairage pens, a procedure combining the use of detergent, followed by a chlorocresol-based disinfectant and a final drying step of 24 h, was the most effective [83]. Though not suitable for food-contact surfaces, chlorocresol can be used in lairage pens in abattoirs as these areas only receive live animals. *Salmonella*-free lairage pens are extremely important to reduce cross-contamination in the beginning of the process; nevertheless, the following steps also have a significant impact on the carcass hygiene. While some slaughtering processes can reduce *Salmonella* carcass contamination, namely scalding and singeing, others can promote carcass contamination, including inefficient scalding, dehairing, polishing, evisceration, and dressing activities [84]. Accordingly, not only should there be good hygiene and manufacturing practices during slaughter and carcass preparation, but also a special attention should be given to C&D of the slaughter line equipment avoiding the possibility of *Salmonella* biofilm formation and environmental persistence.

As for pigs, the poultry slaughterhouses are a decisive step for *Salmonella* contamination. The poultry abattoir scenario has some major differences when comparing with pigs: the animals are moved in crates or cages, and they are not placed in pens before slaughtering, also the slaughter line is almost entirely mechanized and the slaughtering procedures are automated allowing to process, in some broiler abattoirs, up to 15.000 birds per hour. The transport crates and the slaughter equipment have been pointed as possible sources for *Salmonella* contamination [85, 86]. Poultry should only be transported from the farms to abattoirs in clean and disinfected crates. Though C&D reduces the numbers of *Salmonella* present in crates, persistence can be due to the presence of biofilms, improper application of biocides, recontamination, or even cross-contamination [87]. The slaughtering process of poultry encompasses different mechanized steps in intricate equipment, namely scalding, defeathering, evisceration, and chilling, which can ultimately increase the chances of *Salmonella* contamination [87]. The use of standard C&D protocols can in some cases fail to fully eliminate equipment contamination, namely from the plucking machine, after slaughtering *Salmonella*-positive flocks leading to the cross-contamination of *Salmonella*-free flocks slaughtered afterward [81].

Food safety is, and should always be, a top priority issue for food processing industries. Good hygiene and manufacturing practices along with a HACCP plan are essential for obtaining safe animal products. In order to maintain bacterial contamination levels, including *Salmonella*, in the working areas as low as possible C&D must be carried out routinely and effectively. The most relevant biocidal compounds used in the food industry are halogens, peroxygens, acids, and QACs [88]. Regarding egg packing centers, Wales, Taylor, and Davies have recently provided a review on the disinfectants allowed to be used on those facilities, namely QACs, amphoteric surfactants, non-ionic surfactants, sodium hypochlorite, and ancillary agents [89].

The persistence of *Salmonella* in food processing environments, mostly due to biofilm formation, specifically in food-contact surfaces and equipment, after C&D can be associated with insufficient procedures [88, 90]. Additionally, *Salmonella* biofilms in food processing facilities can be a serious problem as biofilms formed in food-contact surfaces can turn out to be a continuous source of food contamination [91]. Despite the multiple reports available on the efficacy of different biocidal substances or formulations on *Salmonella* biofilms under laboratory conditions, studies focusing on the application of such biofilm treatments on food processing facilities are lacking.

Though not applicable in the EU, some countries allow the use of biocides on raw meat/carcasses for decontamination purposes, some examples are provided. In the USA, the use of sodium hypochlorite, peroxyacetic acid, cetylpyridinium chloride, trisodium phosphate, among others, during immersion chilling is preconized for antimicrobial treatment of poultry carcasses [92]. For pig carcasses, the possibility of chemical decontamination seems to be mainly limited to the use of organic acids, namely acetic and lactic acid [93].

The increase of the application of antimicrobial biocides along the food chain was mainly impelled on the one hand by the implementation of stricter food safety regulations and on the other by consumers' requirements. The possible impacts of such a change are still being studied, but some of the unintentional side effects are already clear.

5. Possible implications of antimicrobial biocide usage

As with any other biologically active substance, the application of antimicrobial biocides in multiple settings raises concerns due to the possible implications on human, animal, or environmental health. Subsequently, there are legal requirements enforcing an environmental impact assessment and an authorization by the competent authorities before issuing a license for marketing new biocides or biocide formulations [3, 32]. Nevertheless, the usage of antimicrobial biocides is not deprived of risks, namely their toxicity to humans or the tendency to allow the establishment of biocide resistance [94]. Some antimicrobial biocides can be highly reactive with other substances or can produce direct toxic effects or sensitization on users after dermal or respiratory exposure [95–97]. Additionally, as part of their mechanism of action, these are non-selective compounds and thus can affect multiple organisms other than the intended but can also remain active in the environment after use since they are not easily biodegradable [25]. These characteristics are associated with the presence of biocides in aquatic ecosystems, posing an environmental threat [98]. Furthermore, the improper use of very aggressive antimicrobial biocides or the increase of their dosage to surpass resistance situations increases the possible negative impacts of biocide usage on public health [32]. In fact, the most commonly studied implication of antimicrobial usage is the upsurge of resistances either to antimicrobial biocides or cross-resistances with antibiotics. Any type of resistance to antimicrobial biocides or cross-resistances with antibiotics occurring in *Salmonella* must not be taken lightly, as these phenomena can hinder the previously effective C&D protocols and antibiotic therapeutics whenever necessary in severe salmonellosis cases in humans.

5.1 *Salmonella* resistance to biocides

The effectiveness of C&D protocols to eliminate or reduce *Salmonella* is mainly based on the antimicrobial activity of biocidal substances; thus, resistance to biocides can render the disinfection step useless. A brief overview regarding *Salmonella* antimicrobial biocide resistance is provided along with the possibility of antimicrobial resistance co-selection.

In the literature, multiple definitions for biocide resistance can be found, though perhaps the simplest definition is resistance occurs whenever bacteria survive after biocidal exposure in practical use [99]. The use of other terms such as reduced tolerance or reduced susceptibility as a synonym for resistance is also frequent and is based on increases of the minimum inhibitory concentrations or the minimum bactericidal concentrations, which are assessed under laboratory conditions, and such changes might not have any practical significance [2]. In fact, the bacteria ability to survive is not only dependent on the conditions in which the disinfectant is applied, namely concentration and physical state, but also on bacterial characteristics and on environmental settings [100]. As reviewed by Maillard (2018), after biocide exposure, the stress induced in bacteria leads to the expression of different mechanisms in an attempt to avoid irreversible damage and cell death. These mechanisms include the decrease of the concentration of the biocide in bacteria, either by reducing its penetration, by means of efflux pumps or enzymatic degradation, by physiological or metabolic changes or due to mutations [2].

Apart from the presence of the outer membrane with the lipopolysaccharide layer, characteristic of all Gram-negative bacteria, which acts as a blockade to the entry of unwanted substances, it seems that the major mechanisms for *Salmonella* biocide resistance rely on efflux and enzymatic degradation of biocides as well on mutations on biocide targets and overexpression of target proteins [101]. Among the various mechanisms, the AcrAB-TolC efflux system is the best studied in *Salmonella* and has been associated with resistance in different studies under controlled laboratory conditions [102–104]. Still, biocide-resistant *Salmonella* isolates recovered from field studies are thought to be uncommon [101].

Some of the most conclusive reports on *Salmonella* biocide resistance originating from livestock have been reviewed by Wales and Davies, focusing not only on resistance to numerous biocides but also on the possible co-selection of antibiotic resistance arising from biocide exposure [105]. It is assumed that biocide use can select antimicrobial resistant strains either by picking out biocide resistant bacteria with resistance determinants and mutations also responsible for antimicrobial resistance (cross-resistance) or by selecting bacteria with mobile genetic elements which encode several resistance determinants, simultaneously to biocides and antimicrobials (co-resistance) [34]. Despite the studies suggesting that such co-selection can occur [102, 106, 107], which can eventually have an impact in antimicrobial therapy, the conditions arranged in laboratories are supposed to be different from those observed in real-world practice and thus not accurate models to understand biocide interactions with bacteria in the environment [105]. The actual impact of biocide resistance is not fully understood, and it could be almost as important as antimicrobial resistance, making it a focus for future research [108].

6. Conclusions

The review presented has emphasized, in an uncomplicated manner, the usage of biocides to control *Salmonella* in the food of animal-origin production chains, mainly on poultry and pigs as the major sources, and the possible implications of using these antimicrobial biocides to control this foodborne pathogen, from feed to food or in other terms, from farm to fork.

The use of biocidal substances for disinfection purposes is critical for food safety purposes regarding the control of *Salmonella* along the complex food chains, which supply consumers nowadays. The correct implementation of C&D procedures must always take place in order to reduce the possibilities of *Salmonella* persistence in the environment, a major factor for cross-contamination. It is clear that, in most cases, failure to eliminate *Salmonella* is mainly associated with incorrect usage of biocides rather than a biocide resistance situation. The actual extent of biocide resistance in multiple bacterial pathogens from environmental and food samples should be studied, aiding for a rational usage of these substances or formulations. Nevertheless, with multiple biocidal formulations available in the market, there are several viable options to choose from, considering the different scenarios presented. Furthermore, the development of new biocide formulations, either based on phytochemicals or in nanoparticles ensuring an improved release of the antimicrobial active substances within the intricate structure of biofilms, seems to be promising. Whenever unsuccessful C&D is detected, all steps of the process must be revised, considering the possibilities of improper cleaning, human error on manipulation and application of the biocide, and finally, rotation of biocidal substances or formulations if needed.

Biocide use should not be looked as a panacea for *Salmonella*-associated food safety issues, but together with rigorous control and eradication programs at the herd level, good hygiene and manufacturing practices starting at feed mills up to the food processing industry, and even at the houses of consumers, the burden of salmonellosis in humans can be diminished. Likewise, the scientific community and the competent authorities should also raise the awareness of the consumers toward the possible impacts of the massive usage of household biocidal products as surrogates for good handling and hygiene practices.

This is a continuously growing field of knowledge to which multiple scientific areas are contributing. Further studies, both laboratory and field-based, are required so the most efficient, cost-effective, and safe disinfection protocols can be implemented in the several scenarios where they are irreplaceable.

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Conflict of interest

The authors declare no conflict of interest.

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