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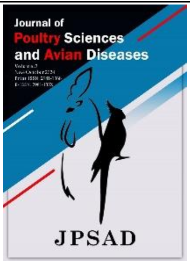

Public Health Impact of Staphylococcal and Clostridial Infections of Poultry: A Comprehensive Review

Peyman Nakhaee[1], Hafez Mohamed Hafez[2]*

[1] Department of Clinical Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran
[2] Former Head of the Institute of Poultry Diseases, Free University Berlin, Germany

*** Corresponding author email address**: hafez@vetmed.fu-berlin.de

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A B S T R A C T

Staphylococcus aureus causes staphylococcal food poisoning and several difficult-to-treat infections in humans. The occurrence and dissemination of methicillin-resistant *S. aureus* (MRSA) is crucial and well documented in various studies. MRSA is an increasing public health concern worldwide. In addition, *S. aureus* is resistant to commonly used antibiotics in poultry farms, which is a concern to public health because of the transmission of this bacteria after consuming poultry meat. Hence, these highlight the significance of antimicrobial and enterotoxigenic monitoring of *S. aureus* in food chains. *Clostridium perfringens* is a ubiquitous spore-forming anaerobic pathogen that causes broilers' clinical or subclinical necrotic enteritis. At the same time, in humans, it is the causal agent of foodborne diseases, frequently related to the consumption of chicken meat. Moreover, enterotoxin-producing *C. perfringens* has high zoonotic potential as well as serious public health concerns due to the emanation of foodborne intoxication. The high diversity and occurrence of *C. perfringens* and *S. aureus* strains indicate the need to carry out various plans to control *C. perfringens* and *S. aureus* associated with foodborne infections. Meanwhile, clinical importance is assisting in understanding the occurrence, source, reservoir, and evolution of antibacterial resistance of *C. perfringens* and *S. aureus* to establish the control of these pathogens.

Keywords: *C. perfringens, Foodborne diseases, Poultry, Public health, S. aureus*

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1 Introduction

Staphylococcus, a genus of Gram-positive bacteria, encompasses several species, with Staphylococcus aureus and Staphylococcus epidermidis being the most commonly implicated in poultry infections. These bacteria can cause a spectrum of diseases ranging from mild skin infections to more severe systemic diseases in the poultry population. Staphylococci are commonly found in the environment, including animals' and humans' skin and mucous membranes (1, 2). While many species of Staphylococcus exist, Staphylococcus aureus and Staphylococcus epidermidis are among the most frequently encountered in poultry environments (3-5). These bacteria can lead to various bird infections, including skin and soft tissue infections, respiratory tract infections, and systemic diseases (2, 3, 6, 7). Staphylococcus infections cause significant challenges to the poultry industry worldwide, affecting bird health and productivity (6, 8, 9). Diverse factors, including management practices, environmental conditions, and other predisposing diseases, influence the occurrence of Staphylococcus infections in poultry. In commercial poultry production systems, high stocking density, suboptimal or low ventilation, and incomplete sanitation and biosecurity can provide favorable conditions for the proliferation and transmission of Staphylococcus spp. among birds (7, 10, 11). Additionally, stressors such as transportation, handling, and high-density housing can compromise the immune function of poultry, increasing their susceptibility to bacterial infections (4, 12, 13).

Staphylococcal infections in poultry manifest in various forms, including dermatitis, cellulitis, bumblefoot, omphalitis (yolk sac infection), arthritis, and respiratory tract infections. These infections can lead to significant economic losses for poultry producers because of decreased growth rates, impaired feed conversion efficiency, increased mortality rates, and costs related to veterinary treatments and interventions (8, 9, 11, 14, 15). Moreover, Staphylococcus aureus, in particular, poses a notable public health concern due to its zoonotic potential (7, 9, 15-17). Staphylococcus aureus infection in human occurs through direct contact with infected birds or their contaminated products, leading to a range of infections, including skin and soft tissue infections, respiratory tract infections, and foodborne illnesses (3, 6, 15, 18). Furthermore, the emergence of antibiotic-resistant Staphylococcus strains in poultry populations raises additional concerns regarding the effectiveness of antibiotic therapies for both animal and human health (9, 15, 18-23). Effective prevention and control strategies are paramount because of the multifaceted nature of Staphylococcus infections in poultry (24, 25). This necessitates implementing comprehensive biosecurity measures, including strict hygiene protocols, routine surveillance, appropriate antibiotic stewardship, and management practices to minimize stress and optimize flock health (6, 9, 15, 16, 25-28). By investigating these factors, poultry producers can mitigate the impact of Staphylococcus infections on bird welfare, productivity, and public health, thereby ensuring the sustainability and profitability of the poultry industry. *Staphylococcus aureus (S. aureus)* is a significant zoonotic pathogen that can cause disease in humans and animals (3, 29). It is widely distributed in nature and is present in air, water, and feed; it also exists on the surface of the human body, in the nasal cavity, on animal fur, and in the digestive tract, among other sites. *S. aureus* has been responsible for several infectious diseases, including tissue and skin infections, pneumonia, sepsis, mastitis, arthritis, and soft tissue infections (3, 5, 30-32).

Clostridium species are Gram-positive, rod-shaped bacteria that thrive in anaerobic conditions. A hallmark of these bacteria is their ability to form endospores, which are highly resistant to environmental stresses, including heat, desiccation, and disinfectants (33-35). This spore-forming capability allows *Clostridium* to persist in the environment, contributing to the difficulty in controlling infections within poultry systems. They are commonly found in soil, decaying organic matter, and the gastrointestinal tract of animals, where they play roles ranging from benign commensals to serious pathogens (34, 36). Clostridium infections represent a significant challenge in poultry production, affecting the health and productivity of commercial poultry flocks worldwide (37, 38). The causative agents are various species within the genus *Clostridium*, anaerobic, spore-forming bacteria known for their pathogenic potential and environmental resistance (34, 39). These infections can lead to severe diseases such as necrotic enteritis, gangrenous dermatitis, botulism, and ulcerative enteritis, each characterized by distinct clinical manifestations and substantial economic impacts (34, 40-42). The transmission of *Clostridium* infections occurs primarily through the ingestion of spores from contaminated feed, water, or litter. These spores can germinate and proliferate in the gut under favorable conditions, such as disrupted gut flora, dietary changes, or environmental stress. Horizontal transmission within flocks is common, especially in intensive production systems with high stocking densities (34, 43). *Clostridium* infections such as Necrotic Enteritis (NE) have remarkable economic implications due to high mortality rates during outbreaks, which result in substantial financial losses, poor feed efficiency, lower growth rates, reduced egg production, increased expenses related to medications, veterinary care, and enhanced biosecurity measures and infected birds suffer from severe symptoms, raising ethical and welfare concerns. Clostridial diseases in poultry production have profound economic and welfare impacts, and high mortality rates during outbreaks can lead to substantial financial losses due to loss of production and the need for carcass disposal (34, 38, 44). Meanwhile, infected birds often exhibit poor feed efficiency, reduced growth rates, and lower egg production, affecting overall productivity and profitability (45-47). Other implications of clostridial infections in the poultry industry are increased expenses for medications, veterinary care, and enhanced biosecurity measures, contributing to the economic burden and significant suffering in affected birds, leading to ethical considerations and potential regulatory scrutiny (38, 48).

2 Prevalence and Risk Factors

Staphylococcus species are ubiquitous in poultry environments, with *S. aureus* being the most clinically significant. Other species, such as *S. epidermidis* and *S. hyicus*, are also encountered, although they are less pathogenic (16, 49, 50). Various factors, including geographical region, type of poultry, age, and production stage, can influence the prevalence of Staphylococcus species in poultry. Various studies demonstrated a widespread prevalence of *S. aureus* and other *Staphylococcus* species in poultry farms across various regions, often exceeding 50% in some areas. A global review reported *that S. aureus* prevalence ranges from 20% to 80% in commercial poultry operations. (2, 6, 18, 51-53). Due to their intensive farming conditions, broilers often exhibit higher prevalence rates of *Staphylococcus* infections. In another study, several studies reported 30% to 80% prevalence rates depending on farm management and biosecurity practices (5, 9, 16, 30, 54). Researchers reported that the carriage rate of *S. aureus* among broilers on all farms was 84.8%, whereas it was 84% among farm workers. The differences in the incidence rates of *S. aureus* in broilers and broilers farm workers in all farms were statistically non-significant (55). In poultry, the most common type of infection is tenosynovitis and arthritis (7, 56). Staphylococcus infections occur mainly during the following four periods of a breeder's life. Omphalitis and femoral head necrosis often relate to egg or hatchery contamination and minor surgeries during the first two weeks of life. Other lesions related to the staphylococcus infection are infected hock and stifle joints secondary to coccidiosis or harsh vaccine reactions. The milder forms of gangrenous dermatitis are generally caused by S. aureus (7, 57, 58). The organism must enter the circulatory system to cause disease; thus, any injury or lesion increases the possibility of disease. The most evident route of infection is through a break or injury in the skin, respiratory tract, and gut (7, 9, 58, 59). *S. aureus* has been able to adapt rapidly to several antibiotics, leading to the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA can resist various types of antibiotics, like β-lactams and others. After a decade, MRSA had been found in many countries that had been considered as an endemic in the mid-1970s (1, 6, 18, 60-65). The detection frequency of 25.9% on turkey farms relates to the results of the National Zoonosis Monitoring 2010, which found that 19.6% of farms were positive (7, 66, 67). In a regional study in the southwest of Germany, researchers found that 90% of the turkey farms were positive for MRSA (68-70). Limited data on the prevalence and epidemiology of MRSA in broiler flocks have been available so far. Out of 384 dust and fecal samples originating from broiler fattening farms, only 0.7% were suspected to be MRSA positive, and they discovered a significant proportion of diseased flocks (55, 71, 72). Other studies in different countries also had varying results, with 35% of flocks positive at slaughter in Denmark and 4 of 50 flocks positive in the Netherlands (61, 62, 65). In another study, the researchers found that 2 of 14 Belgian farms were positive for MRSA by sampling five broiler chickens at each farm (65, 73). Meanwhile, MRSA has been detected in chickens and turkeys from farms and slaughterhouses (12, 60-62, 74-76). LA-MRSA is a distinct spread of specific MRSA clones (ST-398) that colonizes various food animal species (including livestock and poultry) and may be associated with human infection. Risk groups and modes of transmission of livestock-associated MRSA (LA-MRSA) include persons with direct contact with MRSA colonized or infected livestock, such as veterinarians, meat vendors, farmers, workers at slaughterhouses, contact with many different animal products (62, 64, 77). LAMRSA isolates have been detected in meat in different geographic areas, raising concerns about the possibility of transmission of MRSA from the farm to the fork (12, 61, 62, 76). However, human MRSA strains (human-associated and community-associated MRSA) have also been discovered in poultry meat, indicating inappropriate hygienic and sanitary conditions during slaughter or meat processing from poultry meat (6, 62, 78).

C. perfringens could cause reduced production performance in chickens. The intestinal function is to attain optimal feed conversion ratio (FCR) in which several factors reduce this index, such as the necrotic gut lesion and abnormal clostridium dominance in gut microflora together with clostridium toxins, all this reduced productivity (45, 79-81). Immunosuppression predisposes poultry, especially broiler chickens, to NE; immunosuppression likely changes the intestinal environment and commensal flora population (82-84). The recent shift to no antibiotics ever production has elevated the prevalence of Clostridium-related disease. The removal of antibiotic growth promotors (AGPs) has increased the mortality in no antibiotic ever broiler production by 25 to 50%, compared to conventional production (38, 85). With a high incidence of clostridial disease and mortality rates, it is vital to comprehend the prevalence and virulence specifications of *C. perfringens* within broiler flocks. Most diseases caused by *C. perfringens* are mediated by one or more toxins (86). *C. perfringens* is classified into seven toxigenic types, A to G, based on the production of six major toxins: alpha (α), beta (β), epsilon (ε), iota (ι), enterotoxin (CPE), and NetB (86-88). All toxigenic types of *C. perfringens* produce the α toxin encoded by the *cpa* gene. Additionally, type B produces β and ε toxin; type C produces β toxin; type D produces ε toxin; type E produces ι toxin; type F produces CPE, and type G produces NetB (38, 79, 80, 82, 84, 86-88). One or more *C. perfringens* toxins mediate these diseases. Gastrointestinal infections in humans and animals have been indicated to be related to *C. perfringens* type C. In contrast, other toxins have been demonstrated to cause disease in humans or animals, but not both. Type A is the most frequent ofseven *C. perfringens* toxinotypes. However, type F is the one that causes food-related poisoning in humans (38, 80, 89). NE occurs in broiler chickens between the ages of 2 to 6 weeks and in layers of 12–24 weeks due to the reduced titer of maternal antibodies to the clostridial infections with clinical or subclinical manifestations. Outbreak of NE is frequently detected in broiler flocks kept on deep litter, which may be a source of infection (34, 41, 43, 82, 90-93). Clinical NE in poultry is identified by sudden increased mortality without premonitory signs, whereas a subclinical form is frequently related to poor weight gain and feed conversion ratio (47, 88, 91). The development of NE is not exclusively created by infection with *C. perfringens*; predisposing factors, including diets high in non-starch polysaccharide grains and fish meal protein, as well as protozoal infection, have been demonstrated to have an impact on the incidence of NE (93-95). Over the years, antimicrobial agents have been used as growth promoters known as antibiotics growth promoters (AGP) and to control NE in poultry (82, 90, 92, 94-97). However, the prohibition of the usage of AGPs by the European Union in 2006, strict regulations, and voluntary withdrawal of AGPs to struggle with antibiotic-resistant bacteria strains and high consumer demand for antibiotic-free meat had led to the recurrence of NE in poultry (82, 92-94).

3 Antimicrobial Resistance

Methicillin, a new antibiotic with resistance to β-lactamase, was developed two decades later, in 1960, and in less than two years, the first methicillin-resistant *S. aureus* (MRSA) appeared. The term LA-MRSA is distinguished by the spread of certain MRSA clones (ST-398) that colonize various food animal species (including livestock and poultry) and may be associated with human infection (62-64). Risk groups and modes of transmission of livestock-associated MRSA (LA-MRSA) include persons with direct contact with MRSA colonized or infected livestock, such as veterinarians, meat vendors, farmers, workers at slaughterhouses, contact with many diverse animal products and transporters of livestock (60-62, 64, 98). *S. aureus* can adapt rapidly even during selective antimicrobial pressure, which caused the emergence of methicillin-resistant *S. aureus* (MRSA). Resistance to methicillin and other b-lactam antibiotics is due to the *mecA* gene or its *mecC* homolog, located in a mobile genetic element called the staphylococcal chromosomal cassette (65, 76, 99). MRSA has become a threat to public health because, globally, it causes infections associated with hospitals, general communities, and LA-MRSA (100, 101). Various antimicrobial agents such as β-lactamases, macrolides, aminoglycosides, and tetracyclines are widely used in poultry flocks for the prevention and treatment of staphylococci and other infections, which result in the development and emergence of drug-resistant strains of bacterial microorganisms (7, 22, 64, 102, 103). Another significant challenge facing human health is antibiotic resistance. The occurrence of antibiotic-resistant foodborne pathogens is also increasing because of their excessive use in human and animal treatments (14, 15, 18, 23, 104). Moreover, the determinant factors of antibiotic resistance can be transferred to other pathogenic bacterial agents, which can compromise the treatment of serious bacterial infections and, thus, create a great threat to public health (14, 23, 50, 99, 103, 104).

The prevalence of MRSA in animal samples from the prescreened farms averaged between 61.7% and 80% in turkeys and 50% and 54.2% in boilers, respectively. In a study, researchers identified 0% and 28% MRSA-positive animals on three broiler farms (51, 105). Other studies revealed a prevalence of only 6.9% in chickens at abattoirs and 4.4% after investigating pooled throat swabs from multiple broiler farms (6, 64, 106). In analyzing dust and fecal samples from broiler farms in Germany, only 0.7% were suspected to be MRSA-positive (71). Studies in other European countries also had different results, with 35% of flocks positive at slaughter and 8% during rearing (18, 63, 73, 99, 100, 107). In another study, the researchers found that 2 of 14 Belgian farms were positive for MRSA by sampling five broilers at each farm (108). Several studies demonstrated more resistance of *S. aureus* isolates to ciprofloxacin, 92.9% and 50% resistance of tetracycline and ampicillin, respectively. Meanwhile, other researchers reported 100% resistance in *S. aureus* isolates from poultry meat against tetracycline and 61.5% against methicillin in Nigeria (10, 109). They stated 46.2% and 15.4% resistance against chloramphenicol and ciprofloxacin, whereas 38.5% against gentamicin and sulfamethoxazole/trimethoprim. Multidrug-resistant *S. aureus* has been reported several times (78, 110, 111). In addition, several studies reported 59.2% tetracycline to *S. aureus* isolates from ready-to-eat food (112-114). Extensive antibiotic use is thought to be the major cause of drug resistance in foodborne pathogens. The high rate of antimicrobial susceptibility may be due to the low use of these antimicrobials in layer breeders compared with broiler breeders or broilers. Although *S. aureus* is implicated in human food poisoning, most poultry strains do not produce the enterotoxins that cause human foodborne disease (18, 107, 108, 110, 111, 113, 115).

With extensive antimicrobial agents, especially antibiotics, *S. aureus* resistance has indicated an increasing trend recently, which brings great challenges for the clinical treatment of infectious diseases (18, 50, 100, 104, 116). MRSA is a remarkable concern that causes severe morbidity and mortality worldwide (14, 18, 30, 31, 50, 51, 60, 61, 63, 64, 73, 99, 100, 104, 115, 116). More and more molecular epidemiological studies have demonstrated that there are diverse sources of MRSA strains, including hospital-associated MRSA (HA-MRSA), community-associated MRSA (CA-MRSA), and LA-MRSA, indicating that continuous surveillance and screening are essential to discovering modifications in the epidemiology of MRSA infection in humans and animals (18, 73, 99, 107, 117). *S. aureus* is an opportunistic pathogen capable of causing severe disease to farm workers and domesticated animals (14, 55, 118). *S. aureus* is prone to obtaining resistance to many kinds of antibiotics. In the early 1940s, the concept of resistance of *S. aureus* strains to antibiotic therapy was raised, and the prevalence of antibiotic resistance has significantly increased in recent decades because of the excessive use of antibiotics and the prescription used for therapeutics of diseases (14, 55, 118). Since 1959, penicillin-resistant *S. aureus* infections have been successfully treated with methicillin. However, in 1961, several reports from the United Kingdom demonstrated that *S. aureus* strains had been resistant to methicillin. This was the first discovery of the methicillin-resistant *S. aureus* strains (18, 106). *S. aureus* isolated from poultry has become a serious zoonotic risk factor on a global scale for the farm workers groups who handle or live in close proximity to chickens (6, 13, 55, 60, 62). An increasing series of evidence proved that livestock workers are a high-risk population for LA-MRSA carriage because of regular close contact with animals, especially in farm-intensive areas (60, 99). The primary result was LA-MRSA colonization among study participants who had close contact with livestock, identified by LA-MRSA strain isolated from nasal, oropharyngeal, or axillary samples (18, 60, 61, 64, 73, 119, 120). The risk of developing LA-MRSA colonization among livestock workers and veterinarians is also influenced by other risk factors, including livestock density and the type of farm or stage of animal production, history of antimicrobial consumption, hospital admission, working on farms with MRSA-positive animals, flock size and sanitary conditions (101, 119-121). Currently, MRSA strains have been identified using the biochemical test to detect the phenotypical characterization of MRSA, which showed resistance to all the antibiotics that have been produced.

A very significant challenge is the continuous antibiotic resistance of *C. perfringens* strains. Not only is antimicrobial use associated with high antibiotic resistance among bacterial microorganisms, but selection due to utilization of antibiotics may also contribute to a positive or negative relationship with virulence determinants (39, 122, 123). Resistance and virulence may not frequently be independent properties, and their relationship may play a vital role in the pathogenesis of *C. perfringens* infection (38, 80, 122, 123). AGPs were the major intervention strategy against Clostridium infections in commercial broilers (38, 41, 44, 80, 87, 124, 125). This therapeutic protocol supports birds by direct bactericidal and bacteriostatic effects, modifying the gut microbiota, decreasing GIT inflammation, and improving the overall physical health of the GIT (45, 47, 80, 86, 112, 122, 126). However, due to concerns about occurrence of antimicrobial resistance, poultry farmers and veterinarians have limited their antibiotic usage. In 2011, the annual Agricultural Resource Management Survey inferred that 48% of grow-out operations raised poultry, especially broilers, without antibiotics usage and only provided antibiotics when birds suffered from bacterial infections (123, 126-129). Recently, it was estimated that more than 50% of the industry raises broilers without antibiotics. This type of broiler production is referred to as no antibiotics ever (NAE). Broilers reared within NAE facilities cannot receive antimicrobials in feed, water, supplementation, or injection at any part of the bird's lifetime. (130-132). The potential increase in the antimicrobial resistance of *C. perfringens* has occurred recently, with several reports declaring that most *C. perfringens* were multidrug-resistant (MDR) isolates (39, 133, 134). The resistance to tetracycline through TetA(P) protein, which regulates tetracycline active efflux, was common. In addition, over 50% of *C. perfringens* isolates were resistant to lincomycin. However, 25% of this resistance was related to the expression of the *lnu* gene (39, 134, 135). It should be noted that higher minimum inhibitory concentration (MIC) values of amoxicillin and ciprofloxacin were recorded due to the presence of the β-lactamase (*bla*) and quinolone (*qnr*) resistance genes, respectively. In the same context, the macrolide-resistant *C. perfringens* may act as reservoirs for the *erm* gene, which assists in its conjugal transfer (39, 122, 123, 135-138).

Previous studies have shown that tetracycline resistance is the most common antimicrobial resistance phenotype observed in *C. perfringens* and that it is related to the use of antibiotics for the treatment and as growth promoters in food animals. As a result, antimicrobial resistance of *C. perfringens* to tetracycline, lincomycin, and erythromycin has increased significantly over the past three decades (20, 28, 39, 45, 111, 122, 123, 139, 140). *C. perfringens* induces a toxico-infectious foodborne sickness, in which infection by viable bacterial cells and their toxins plays a significant role in creating gastroenteritis in the host (34, 141). *C. perfringens* infections cause gas gangrene, necrotizing enteritis, and food poisoning in humans and animals. In order to minimize and decrease the economic losses induced by these infections, many antimicrobials, such as ampicillin, tetracycline, chloramphenicol, metronidazole, and imipenem, have been used preventively in the livestock industry (19, 22, 39, 80, 89, 103, 134, 135). Despite increasing awareness of the importance of combating antimicrobial resistance to improve public health, resistance of *C. perfringens* from various sources to different antibiotics has yet to be actively investigated. The long-term and frequent use of antibiotics in the livestock and poultry industry has increased antimicrobial resistance in *C. perfringens*, compromised the efficacy of antibiotics, and generated great difficulties in clinical treatment (20, 39, 122, 139, 140). Probiotics are extensively used microorganisms to deal with particular diseases such as avian subclinical NE. The efficacy of probiotics belonging to the genera *Bacillus*, *Lactobacillus*, *Enterococcus*, *Bifidobacteria*, and *Saccharomyces* has been assessed both in vivo and in vitro (80, 92, 96). One of these studies reported a meta-analysis that included independent trials performed in different countries simultaneously, demonstrating in large-scale assessments that the supplementation of probiotics like *B. subtilis* remarkably elevates productive parameters and decreases the histological damage caused by *C. perfringens* (44, 92, 124, 125, 132, 134, 136, 142-144). The composition of the microbiome associated with broilers has been associated with improved production efficiency, representing that the use of probiotics demonstrated a viable alternative to avoid antibiotics in diets. It has been suggested that probiotics may beneficially affect the structure of the host gut microbiota, consequently improving the growth and survival of farm organisms (44, 92, 125, 128, 132, 136, 142-144). In addition to probiotics, other strategies, including prebiotics, synbiotics, organic acids, phytogenic additives, and dietary modifications and enzymes, can be used for the prevention and control of *C. perfringens* in the poultry industry and, more importantly, avoid the occurrence of antibiotic resistance.

4 Public Health Impacts

Foodborne diseases (FBDs) and poisoning are the widespread and great public health challenges of the modern world. Both developed and developing countries are widely affected by foodborne infections. FBDs impact human health and well-being and have economic effects on individuals and countries. Food poisoning outbreaks primarily comprise meat and meat products, but other food items, such as milk, may also be contaminated (145-147). FBDs are pathological cases created by the ingestion of food containing biological, chemical, or physical hazards. Multiple pathogenic bacteria can cause FBD, among which *Salmonella* spp., *Staphylococcus aureus* (*S. aureus*), and *C. perfringens* are the most common pathogenic bacteria in poultry-source foods. (8, 139, 148).

Staphylococcal food poisoning (SFP) is in relationship with emetic activity, sepsis-related infections, pneumonia, and toxic shock syndrome (TSS). *S. aureus* has been frequently isolated from many foodstuffs, such as dairy products and meat. Therefore, it has been accounted as the third largest cause of food-associated disorders worldwide (128, 139, 145). In addition, it is one of the major public concerns since the treatment protocol for infections is a challenge when facing resistance, contributing to the evolution of MRSA. MRSA from poultry meat poses a public health risk that can be transmitted to humans by handling or consuming contaminated poultry meat (127, 139, 140). MRSA in poultry and poultry products is a concern to the poultry industry because of the risk to human health (13, 50, 78, 115, 147, 149, 150). The most important concern is the production of staphylococcal enterotoxins by MRSA strains, which can induce staphylococcal foodborne illness (18, 51, 62, 73, 100, 107). Raw meat handling, cross-contamination, and undercooked meat consumption may lead to MRSA infections. The epidemiology of MRSA in poultry has gained significance in recent years because of the growing demand for high-quality food and improved food safety (151, 152). This demand has led to increased poultry production, processing, and distribution of products, facilitating MRSA creation and spreading all over the food production chain.

The spread of MRSA in livestock is a serious public health threat. MRSA occurs among livestock animals like pigs, cattle, poultry, and companion animals. Interestingly, LA-MRSA also emerged among humans, demonstrating a zoonotic transmission from animals to humans (61, 62, 147, 153). Working and/or living on an MRSA-positive broiler farm was identified as a risk factor for acquiring MRSA. According to previous studies conducted in European countries, approximately 35% of slaughterhouses were MRSA-positive. On the other hand, the researchers recorded a 28% prevalence of MRSA from poultry farms in Malaysia (51, 62, 154). Furthermore, they isolated MRSA from turkey flocks in the Netherlands at 62-80% (6, 73). In Germany, transmission of MRSA from livestock to humans occurred mainly from occupational animal contact (61, 62, 151). Among 466 persons tested for MRSA in Dutch poultry slaughterhouses, 26 individuals were positive, which specifies a higher exposure risk to MRSA compared to the non-occupational Dutch people (155). Furthermore, MRSA has been discovered in various meat products, including turkey, raw chicken, veal, pork, mutton or lamb, beef, and rabbit (3, 18, 154, 156-158). Many authors have referred to detecting MRSA in chickens, cattle, pigs, and dogs. Along with creating cultural awareness of humans worldwide, consumers tend to eat low-fat with high minerals, vitamin contents, good quality protein, quickly prepared, and low expensive chicken meat compared to the other types of meat. However, at the same time, human exposure to food poisoning was increased by consuming contaminated chicken meats with MRSA (3, 9, 14, 18, 64, 73, 158).

Evaluating *S. aureus* prevalence in poultry flocks is important for future risk prediction in poultry production and related occupational risks. Hence, understanding the possible outbreaks in antibiotic resistance through a sustainable surveillance program of the antimicrobial resistance profile of *S. aureus* simultaneously with the medical and veterinary conditions is necessary for the appropriate improvement of *S. aureus* control (18, 149, 154). Regular genotypic analysis of *S. aureus* from human and chicken origin is needed to discover the relationship between them due to the potential for transmitting MRSA to humans by consuming poultry or any by-product containing such *S. aureus* strains. Despite decreased antimicrobial usage in European animal production in recent years, the prevalence of MRSA in farm animals has not reduced (61, 108). It is, therefore, likely that MRSA remains in other reservoirs, such as in humans (i.e., farm workers and veterinarians). Strategies involving reducing the reliance on antibiotic usage and the frequent change of antibiotic classes should be considered for reducing MRSA levels in highly contaminated farms. Control and treatment strategies such as strict preventive biosecurity measures, selective probiotic feeding, and MRSA eradication programs should be used to prevent MRSA outbreaks on a farm, reduce MRSA carriage and eradicate MRSA from contaminated farms, respectively (9, 61, 64, 108, 109, 132, 152, 159).

Approximately 13% of gastrointestinal foodborne outbreaks have been related to *C. perfringens* infections (80, 89, 134). *C. perfringens* foodborne infections are frequently associated with meat and poultry products. The meat products can be contaminated with this pathogen during slaughtering through the contaminated surface or the contact of carcasses with feces (80, 141, 160, 161). Standard food service practices should be pursued to prevent this pathogenic microorganism (82, 84, 134). Chicken meat is the most consumed animal protein, and a sufficient supply for consumers requires mass production strategies, exacerbating the challenge of infections by FBPs such as *C. perfringens*. Because of this, there is a need to find economical, environmentally friendly, and efficient alternatives in the modulation of the intestinal microbiota, which contribute to the efficient production of broiler chicken to meet current and future demand (41, 80, 162). Also, it is recommended to cook food until the internal temperature reaches 70$^{\circ C}$. Notably, gastrointestinal infection with *C. perfringens* in animals and humans occurs due to the production of potent exotoxins (89, 134, 136, 163). As one of the most common foodborne zoonotic pathogens, *C. perfringens* is known to induce a variety of diseases, from food poisoning and slight diarrhea to life-threatening enterotoxaemia and gas gangrene in humans and animals (80, 162-164). Due to the increase in the emerging threat of foodborne-associated *C. perfringens* infections, many investigations demonstrated the prevalence of *C. perfringens* in food chains. They highlighted the evolution hazards of *C. perfringens* and the widespread MDR/toxigenic phenotypes. Several studies have revealed the high prevalence of MDR *C. perfringens*, which is a remarkable threat to the efficient treatment of foodborne illness by restricting the therapeutic options (34, 39, 134, 165, 166). The results of related studies indicated frustrating susceptibility patterns, and the antibiotics used in poultry feed as growth promoters were the main reasons for the evolution of *C. perfringens* resistance patterns as the bacteria became adapted due to the frequent use of antibiotics. Hence, there is an essential need for strict guidelines explaining the use of antibiotics and the safe production of food products of poultry origin (39, 89, 122, 134, 136, 138, 165, 166).

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Conflict of Interest

The authors declared no conflicts of interest.

Author Contributions

All the authors contributed to all parts of this research.

Data Availability Statement

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