Review

Preharvest Control of *Campylobacter* Colonization in Chickens: Special Emphasis on Vaccination Strategies

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Preharvest Control of *Campylobacter* Colonization in Chickens: Special Emphasis on Vaccination Strategies

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Abstract

Campylobacter is a leading cause of human gastroenteritis, with poultry serving as the primary reservoir host. Effective preharvest control strategies are crucial for preventing or reducing *Campylobacter* contamination on meat surfaces. As concerns grow regarding the use of antimicrobials in animal agriculture, the importance of non-antimicrobial preharvest strategies in poultry production has become increasingly significant. This comprehensive review focuses on the biology of *Campylobacter*, its impact on public health, and current and emerging preharvest strategies with a special emphasis on vaccination. Preharvest strategies are broadly classified into biosecurity measures, gut microbiota modifications using prebiotics, probiotics, postbiotics, feed additives, and vaccination. While many live, attenuated, and subunit vaccines have proven effective in research settings, there are currently no commercial vaccines available. Because no single strategy can effectively combat *Campylobacter*, integrating multiple approaches, such as improved biosecurity measures, immunization, and dietary modifications, may provide a solution for reducing *Campylobacter* loads in poultry. Embracing a "One Health" approach, gaining a deeper understanding of *Campylobacter* pathophysiology, making advancements in vaccine technology, and implementing holistic farm management practices will be essential for sustainable control of Campylobacter and for reducing the risk of human campylobacteriosis.

Keywords: *Campylobacter*; chicken; foodborne infection; gastroenteritis; poultry; preharvest control strategies; vaccination; gut microbiota; multifaceted approach; One-Health

1. Introduction

Campylobacter is one of the major causes of bacterial gastroenteritis in the United States [1,2]. Each year, an estimated 1.5 million people in the United States contract *Campylobacter* infections [3]. The primary source of these infections is raw or undercooked chicken meat containing high loads of *Campylobacter* originating from the chicken's digestive tract [4–6]. The two major species responsible for human infections are *Campylobacter jejuni* and *Campylobacter coli* [7]. Apart from causing gastroenteritis, *C. jejuni* is linked to about one-third of Guillain-Barré Syndrome (GBS) cases in humans [8–10]. GBS is an immune-mediated peripheral nerve disease characterized by symmetrical ascending weakness that can progress to paralysis accompanied by hyporeflexia and areflexia [11,12]. Thermophilic *Campylobacter* species, mainly *C. jejuni* and *C. coli*, are commonly found in wild birds and domestic poultry [13–16]. Some farms worldwide have reported *Campylobacter* prevalence rates as high as 100%, particularly among birds that have reached marketable age. Both *C. jejuni* and *C. coli* have adapted to the avian gastrointestinal tract. Despite widespread intestinal colonization (up to 10^9

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colony-forming units/g of cecal content), *Campylobacter* are often regarded as commensals in birds, causing little to no overt illness [4,17–19]. However, recent studies have shown that *Campylobacter* spp. can lead to significant infections and immune responses [20–23]. Following intestinal infection by *Campylobacter* in chickens, cytokine responses that drive humoral, adaptive, and Th17 responses have been observed [21,24,25]. Additionally, the newly emerged species, *Campylobacter hepaticus*, causes spotty liver disease (SLD) in layer hens, which is most prevalent during peak production stages [26,27].

Fluoroquinolones and macrolides have been widely used in the past in animals for growth promotion and infection control purposes. They have also been prescribed as supportive treatments for human *Campylobacter* infections. However, this widespread use in food animals is believed to have significantly contributed to the development of antimicrobial resistance (AMR) against these antibiotics [28–30]. The emergence of AMR has significantly restricted effective antibiotic treatment options for *Campylobacter* infections [30–32]. Consequently, growing concerns regarding AMR and food safety have led to bans on the use of medically important antimicrobials in food production systems for nontherapeutic purposes, driving the urgent search for alternative strategies that focus on *Campylobacter* control and prevention at the poultry farm level [32–36]. Achieving *Campylobacter* prevention in farm settings is quite challenging due to following reasons, i) the ubiquitous nature of *Campylobacter*, ii) multiple transmission routes, iii) a low infection dose required for human illness, and iv) the delayed detection of *Campylobacter* colonization or spread in birds [37–40]. Despite these challenges, quantitative microbial risk assessment studies showed a 1–2 log reduction in the level of *Campylobacter* in broiler chicken intestines can significantly impact relative risk reduction, achieving a decrease of 44%-95% [41]. The incidence of *Campylobacter*iosis through chicken meat can be reduced 30 times by introducing a 2-log reduction in the number of *Campylobacter* spp.in chicken carcasses [42]. Therefore, control of human *Campylobacter* infections is feasible through the consistent application of safe practices from farm to fork.

Campylobacter control strategies can be broadly divided into two main categories: preharvest and postharvest strategies [43,44]. Preharvest strategies are measures and interventions to control *Campylobacter* at the farm level. These strategies mainly focus on reducing *Campylobacter* colonization and preventing its introduction and spread in the environment [34,45,46]. Preharvest strategies can be further divided into three categories: i) reduction of environmental exposure through biosecurity measures, ii) reducing *Campylobacter* colonization in the bird intestines by improving host resistance via competitive exclusion, vaccination, and host genetic selection, and iii) using alternatives to antibiotics to mitigate *Campylobacter* colonization in birds [47]. Post-harvest interventions include carcass decontamination, antimicrobial treatment for poultry processing, cold chain management, and consumer education [48–54]. However, most of these interventions are ineffective when used alone and are not commercially available. While vaccines have shown promising results in the prevention of various poultry diseases, and many studies have tested numerous vaccine candidates, no commercial vaccines are currently available to prevent or reduce *Campylobacter* colonization in chickens. A multifaceted approach that combines two or three strategies, with a particular focus on vaccination, is essential for preventing and controlling *Campylobacter* colonization in poultry. This comprehensive review explores the current state of preharvest approaches to mitigate *Campylobacter* colonization in poultry, with a special emphasis on vaccination strategies against *Campylobacter* spp.

2. Campylobacter in Broilers –Biology and Public Health Impact

Campylobacter spp. are gram-negative, motile, slender, comma-shaped or spiral-shaped, non-spore forming bacteria. They grow strictly under anaerobic to microaerophilic conditions and are nutritionally fastidious organisms. The bacterial length ranges from 0.5-5 μm and width of 0.2-0.9 μm [55,56]. There are more than 57 *Campylobacter* spp. under the genus *Campylobacter* (https://lpsn.dsmz.de/genus/*Campylobacter*). They colonize the intestines of warm-blooded hosts, including humans; however avian species are more favorable as commensal colonizers [57]. In humans, *Campylobacter* causes gastroenteritis, which can sometimes lead to complications such as

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Guillain-Barré Syndrome (GBS), irritable bowel syndrome (IBS), and reactive arthritis [56]. In the United States, *Campylobacter* is one of the major causes of gastroenteritis with approximately 1.3 million cases leading to economic costs ranging from $1.3 to $6.8 billion [58]. Generally, self-limited diarrheal illness lasts for about 5 to 7 days, but elderly people with immuno-compromised status are at a high risk for mortality, morbidity, and prolonged illness [7].

C. jejuni and *C. coli* are the major *Campylobacter* species associated with human illness. Humans acquire infections through fecal-oral transmission from infected animals and food products [59,60]. Avian species, especially chickens, account for 50% -70% of *Campylobacter* infections in humans [61]. When chickens carry *Campylobacter* in their intestines, chicken meat may become contaminated during slaughter and processing [62]. As few as 500 to 800 CFU of *C. jejuni* are sufficient to cause infection implying that bacteria do not need to multiply to cause disease [63,64].

Campylobacter can colonize the mucus of the small intestine and ceca of chickens sometimes at very low densities such as 40 CFU [65]. Once colonization occurs, bacteria rapidly reaches a high number in cecal contents [66–68]. Chicken are coprophagic meaning that they consume feces, which allows contaminated feces to spread Campylobacter rapidly throughout the flock. Once Campylobacter colonization is detected in a flock, most birds in the flock typically become colonized within days [69–72]. There is a direct correlation between Campylobacter prevalence in chickens and the likelihood of human Campylobacter infections. Therefore, reducing the prevalence of Campylobacter in chicken flocks has the potential to significantly decrease human infections [73]. This approach has been quite successful in countries such as Denmark and Iceland [74,75].

3. Overview of Preharvest Control Strategies

Various non-antibiotic interventions have been tested to reduce *Campylobacter* colonization of poultry during the preharvest phase (Figure 1). These include biosecurity measures, prebiotics, probiotics, postbiotics, feed additives, bacteriophage therapy, vaccination, and genetic selection for resistant chicken strains.

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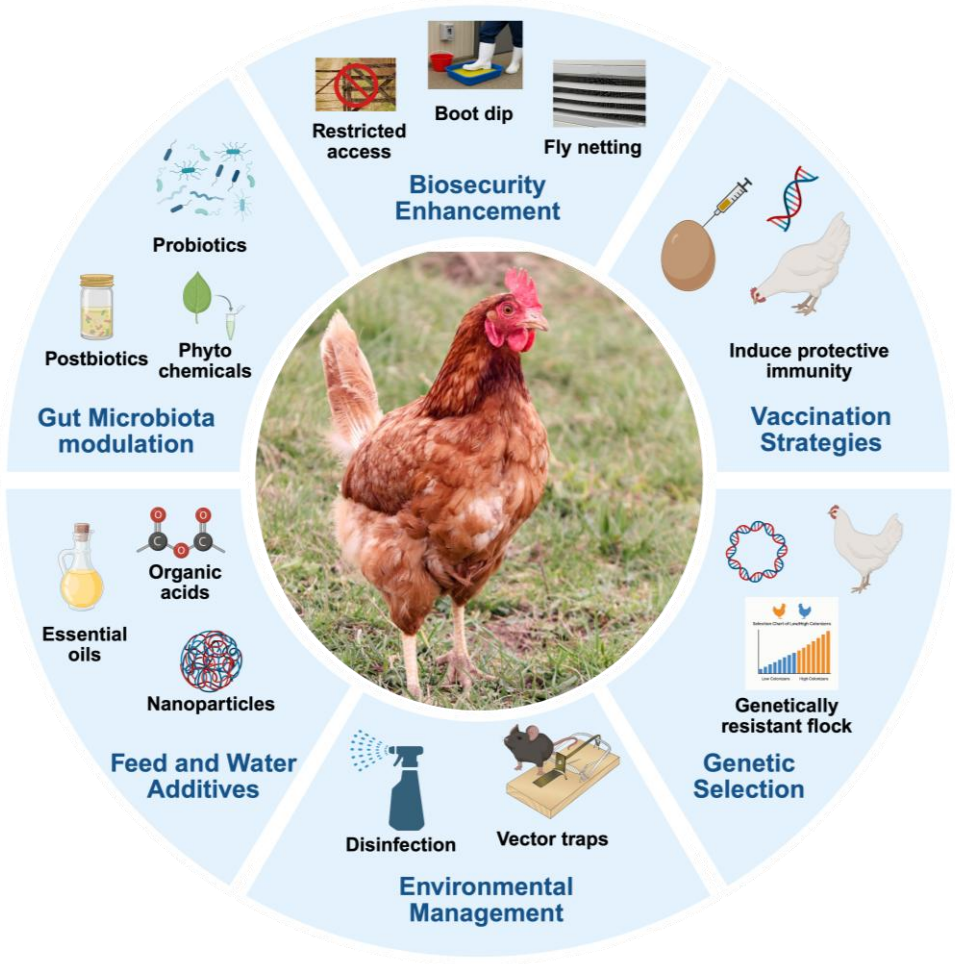

Figure 1. Preharvest intervention strategies to control *Campylobacter* in poultry (Created in BioRender).

3.1. Biosecurity Measures

Biosecurity is crucial for keeping *Campylobacter* out of animal flocks, as it acts as the primary defense against this pathogen [46,76]. In poultry, the transmission route of *Campylobacter* is horizontal (Figure 2). There are no known reports on vertical transmission of *Campylobacter* spp. There are currently no known reports on vertical transmission of *Campylobacter* spp. Potential sources of *Campylobacter* into a farm include, domestic and wild animals, farm equipment, contaminated litter, feed and water as well as potential transmission form infected birds [77–81]. The poultry house interior environment showed a lower prevalence of *Campylobacter* in air/ventilation samples (6%), pests (5%), litter (3%), water samples (2%), and feed (rarely), in the descending order of *Campylobacter* prevalence rates. The external environment of the poultry house showed 14% prevalence, with 67% and 14% prevalence in domestic animals and their excreta, respectively. The transport equipment used for live haul, including trucks (44%) and crates (22%), showed different prevalence rates of *Campylobacter* [78]. Although implementing strict biosecurity measures can be challenging, they are fundamental in preventing initial colonization. Many interventions primarily focus on reducing *Campylobacter* levels after it is already present, but biosecurity protocols help prevent it from entering the farm in the first place. The effectiveness of biosecurity is greatly enhanced when combined with other successful strategies [82,83].

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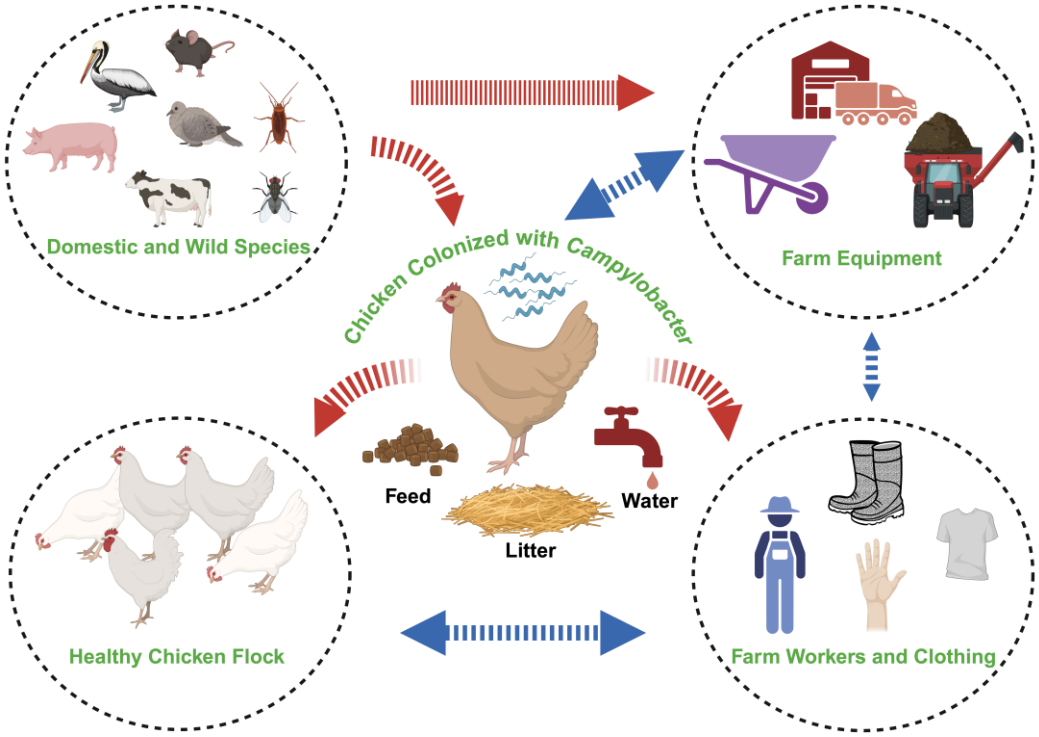

Figure 2. On farm transmission cycle of *Campylobacter* in poultry production (Created in BioRender).

3.1.1. Managing Human Entry and Hygiene to Prevent Contamination

Campylobacter bacteria are frequently found in agricultural workers, farm managers, and truck drivers. To reduce the number of *Campylobacter*-positive flocks, it is recommended to limit human traffic by restricting unnecessary movements of people and minimizing visitors to farms and animal housing. The following practices can help reduce the entry of *Campylobacter* through humans: (i) Enforce the use of personal protective equipment (PPE): PPE should be mandatory for anyone making essential visits to the farm. (ii) Maintain dedicated hygiene measures: Regularly cleaned and disinfected footwear and clothing specifically should be designated for each poultry house. This practice helps create a stronger hygiene barrier. (iii) Promote hand hygiene: Handwashing stations should be accessible at all entry points to the poultry houses. Everyone must be instructed to thoroughly sanitize their hands for 15-20 seconds both before entering and after leaving animal housing. (iv) Avoid high-risk activities: To significantly reduce contamination risks, it is important to avoid unnecessary movements of people, particularly during high-risk activities such as thinning [46,84]. Despite having clear guidelines, biosecurity protocols are often not followed meticulously. To achieve a greater impact, comprehensive training, education, and consistent monitoring are essential to ensure adherence to best practices [83,85].

3.1.2. Equipment and Vehicle Sanitation

The movement of vehicles and equipment between houses or between farms poses a significant risk of *Campylobacter* transmission. It is not advisable to transfer the equipment unless it is properly cleaned. *Campylobacter* can survive longer periods on equipment surfaces, staying in a viable but non-culturable state (VBNC), making it more challenging to eliminate from the environment and allowing it to survive under various stress conditions [86,87]. Residual organic matter still harbors *Campylobacter*, protecting the standard washing process [37]. It is necessary to employ effective sanitation and disinfection methods to prevent the spread of *Campylobacter*. This process involves more than just washing; it requires a multistep approach that includes dry cleaning, wet cleaning, disinfection and drying [82].

3.1.3. Pest and Wildlife Control

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Animals, including cattle and poultry, are known reservoirs of *Campylobacter*, which has been isolated from the intestinal tracts of various animals and birds [88–91]. Wildlife serves as an amplifying host, exhibiting a high pathogen shedding capacity and playing an important role in transmission [77]. Wild birds are particularly important because they can spread *Campylobacter* from different geographical areas because of their ability to fly over large distances [92,93]. In addition to domestic and wild animals, birds, rodents and insects have all been shown to transmit *Campylobacter* [94–98]. To control its spread, robust vector-control programs should be implemented targeting wild animals, rodents, and insects. Comprehensive integrated pest management programs can help eliminate pest attractants and breeding sites from the surrounding environment. Effective strategies include rodent-proofing measures, targeted larvicides for improved litter management to exclude and control flies, and bird-proof sealing to deter wild birds [46,99].

3.2. Probiotics, Prebiotics and Postbiotics

In the post-antibiotic era, there is a growing interest in probiotics, prebiotics, and postbiotics as effective dietary interventions [100,101]. Probiotics are non-pathogenic live organisms that confer health benefits to the host when consumed in adequate amounts [102]. Common probiotic microorganisms belong to the genera Lactobacillus, Bifidobacterium, Saccharomyces, Bacillus, Streptococcus, and Enterococcus [103–106]. They positively influence the host through various mechanisms, such as improved intestinal barrier function, immunomodulation, and production of neurotransmitters [107]. Probiotic supplementation in chicken diets helps maintain intestinal homeostasis, eliminate pathogenic bacteria through competitive exclusion, and stimulates the secretion of important digestive enzymes such as phytases, amylases and proteases, thereby improving feed utilization efficiency [108–114]. Chickens are monogastric animals, that have a single-chamber stomach divided into the gizzard, small intestine, and large intestine [115]. The entire GIT interacts symbiotically with microbiota to aid in digestion and absorption and plays crucial roles in health and production by regulating physiological processes [116–118]. The chicken gut microbiota is highly complex and is dominated by bacteria, with over 600 different bacterial species identified [119]. While bacterial diversity varies throughout the GIT, the cecum is the most densely colonized region. The cecum plays a key role pathogens colonization [120,121]. Under uncertain conditions, an imbalance in the normal gut microbiota can promote the growth of opportunistic and pathogenic bacteria, thereby disrupting gut health. Probiotics can help in this situation by restoring the beneficial gut microflora and preserving gut integrity [120,122–124].

Prebiotics are non-digestible food components, generally metabolized by specific bacteria and provide beneficial effects on the host [121,125]. They help increase the abundance of beneficial microorganisms such as bifidobacteria and lactobacilli and improve gut metabolic activity, resulting in the production of a series of metabolites that favor the maintenance of gut health [121,126]. Prebiotics consist of monomers derived from common sugars, including glucose, galactose, fructose, and xylose. Widely studied examples are insulin, fructooligosaccharides (FOS), isomalto-oligosaccharides (IMO), and galactooligosaccharides (GOS). Postbiotics are functional bioactive molecules produced during the metabolic processes of probiotics, that which confer health benefits to the host [122,127]. Unlike live probiotics, postbiotics offer a safer and more stable alternative by mitigating key limitations that have impeded the broader application of probiotics in commercial settings, such as the risk of antimicrobial resistance, poor thermal stability, and potential for expressing virulence factors [128]. According to the International Scientific Association for Probiotics and Prebiotics (ISAPP, 2021), postbiotics are comprised of inactivated microbial cells, bacteriocins, cell-free supernatants, exopolysaccharides, and short-chain fatty acids [129,130]. A growing body of in vitro and in vivo evidence indicates that postbiotics enhance gastrointestinal health by promoting beneficial bacterial populations, modulating host immune responses, and supporting intestinal barrier integrity [131–134].

3.3. Bacteriophage Application in Campylobacter Control

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The application of bacteriophages as a biocontrol strategy has been investigatedfor controlling food-borne pathogens (e.g., *Listeria*, *Salmonella* and *E. coli* O157:H7 [135]. Bacteriophages are viruses that infect bacterial cells and have demonstrated potential as therapeutic agents against bacteria. Bacteriophages used in these treatments are specific to bacteria. For instance, certain *Salmonella* bacteriophages (ST27, ST29, and ST35) are specific to the TolC receptors of *Salmonella* serovars. The binding specificity of bacteriophages to bacteria determines their host ranges. Upon entering a bacterial cellbacteriophages generally undergo either a lysogenic or a lytic cycle. Bacteriophages utilize the host machinery to produce progeny. Because of the low risk of phage transduction and rapid lysis activity, lytic phages are preferred as therapeutic targets over lysogenic phages. It is estimated that a 2 log CFU reduction in *Campylobacter* levels in poultry intestines is sufficient to reduce the occurrence of human campylobacteriosis associated with poultry by 30-fold [136]. Chinivasagam *et al*., used a cocktail of bacteriophages to control *Campylobacter* in a commercial broiler setting. One of the farms involved in the trial achieved a 1–3 $\log_{10}$ CFU/g significant reduction in *Campylobacter* loads in the ceca of 47-day-old broiler chickens compared to the control group. Another farm in the study showed a non-significant 1.7 $\log_{10}$ CFU/g reduction in *Campylobacter* [137]. Another recent study conducted with a cocktail of two bacteriophages showed a significant reduction of 2.4 $\log_{10}$ CFU g^{-1} in *Campylobacter* two days of post-treatment compared to mock-treated controls [138].

3.4. Feed Additives

In poultry production, organic acids such as acidifiers (e.g., formic, butyric), essential oils (EOs) (e.g., thymol, carvacrol), and diverse plant extracts (phytogenic) are increasingly utilized as alternatives to antibiotic growth promoters. These substances play an important role in enhancing intestinal health primarily by modulating gut microbiota [139,140]. Organic acids are naturally produced during the metabolism of various animal feeds. They help lower intestinal pH, thereby inhibiting the proliferation of pH-sensitive enteric pathogens such as *Salmonella* and *E. coli*. This acidic environment allows the undissociated form of these acids to pass across bacterial cell membranes, leading to intracellular acidification, disruption of metabolic processes, and eventual bacterial lysis, while simultaneously fostering the growth of beneficial acid-tolerant bacteria such as *Lactobacillus* and *Bifidobacterium* [141–143]. Organic acids also aid in the absorption of vital micro- and macro-minerals such as calcium, magnesium and zinc [141]. Eo's are strong antioxidants and antibacterial agents [144]. They are rich in lipophilic phenolic compounds that can disrupt bacterial cell membrane integrity, increase permeability, and cause leakage of cytoplasmic contents, which contribute to their broad-spectrum antimicrobial effects against pathogens such as *Clostridium perfringens* and *E. coli* [145]. EOs can also neutralize free radicals and exhibit potential antioxidant properties [146,147]. Plant extracts are generally considered safe, and many can be consumed as food [148,149]. These extracts comprise of a complex array of bioactive compounds such as flavonoids, tannins, and alkaloids. They exhibit multifaceted mechanisms such as direct antimicrobial effects, anti-inflammatory and immunomodulatory properties that strengthen the gut barrier, and the ability to stimulate digestive secretions, collectively shifting microbial communities towards a healthier and more diverse microbial profile that favors commensal bacteria and optimizes nutrient utilization [150–153]. For example, herbal compounds like tryptanthrin have been shown to significantly reduce *Campylobacter* colonization in vitro and in vivo [154].

3.5. Vaccination – A Targeted Approach

Vaccination is a proven strategy for the prevention and control of bacterial and viral infections. Compared to other management strategies, it offers advantages in terms of public health impact and long-term sustainability [153,155]. Currently, no commercial vaccine is available to protect chickens from colonization [156–158]. Although vaccines are not 100% successful in preventing *Campylobacter* colonization in hens, they have been shown to be more effective than previously reported methods. Better protection could potentially be obtained by combining immunization with additional preharvest strategies [159–161]. Figure 3 illustrates the different vaccine strategies available for the

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prevention and control of bacterial infections. These include killed/inactivated vaccines, subunit vaccines, live attenuated vaccines, DNA vaccines, and mRNA vaccines, each with their own advantages and disadvantages.

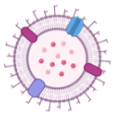
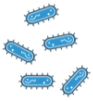
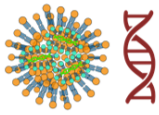
Vaccination strategy	 Killed/Inactivated	 Subunit/Protein	 Live Attenuated	 DNA/mRNA
Antigen source	Killed bacteria	Proteins/Outer membrane proteins	Live bacteria with mutations	Plasmid DNA or mRNA
Immunity	Weak Humoral	Humoral	Humoral and Mucosal	Cell mediated
Advantages	No live bacteria	Safer and target specific	Strong immunity	Easy scalability and No reversion of risk
Disadvantages	Weak immunity	Booster doses required	Risk of shedding	Cost and delivery optimization

Figure 3. Major types of vaccines used to control bacterial infections in poultry (Created in BioRender).

3.5.1. Types of Poultry Campylobacter Vaccines

3.5.1.1. Subunit Vaccines

Subunit vaccines use bacterial components instead of complete bacteria, to trigger an immune response. They generally offer advantages over attenuated and killed vaccines in terms of lower risk of reverting to virulence, enhanced safety, targeted immunity, and better compatibility with adjuvants. Despite these advantages, developing effective subunit vaccines remains a challenge. One major difficulty is identifying suitable antigens capable of protecting different *Campylobacter* species or even serotypes and strains within the same species. Also, providing robust immunity to protect broiler chickens with a shorter lifespan requires an optimized delivery method. To date several antigens tested as subunit vaccines have shown modest to significant results [162–164].

3.5.1.2. Live-Attenuated Vaccines

Live attenuated vaccines are live bacteria that result from reduced virulence/pathogenicity but are capable of generating adequate long-lasting immunogenicity while activating both adaptive and innate immune responses [157,165]. Live attenuated vaccines tested against *Campylobacter* include heterologous bacterial vectors that transport *Campylobacter* antigens and *Campylobacter* strains with mutated oxidative stress defense antigens [157,160]. Another approach to live attenuated vaccines is to use *E. coli* to deliver glycoconjugated antigens, thus improving the vaccine performance [166] . These vaccines offer more advantages than killed and subunit vaccines by providing long-lasting immune responses, including mucosal immunity. Despite these advantages, the risk of reverting to virulent forms and interference with material antibodies in young chickens are major concerns regarding subunit vaccines [167]. Environmental contamination through the shedding of vaccine strains is an additional concern, making it crucial to select a strain that guarantees both safety and immunogenicity without posing any environmental biohazard risks [167,168].

3.5.1.3. Inactivated/Killed Vaccines

The concept behind inactivated or killed vaccines is that, after undergoing physical or chemical treatments bacteria still retain protective antigens that can elicit an immune response [169]. However, few studies on inactivated or killed vaccines have had shown limited success [170–172]. A major challenge with poultry killed vaccines is identifying an effective adjuvant to boost the immune response [173]. Additionally, inactivated/killed vaccines do not generate the mucosal immune

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response essential for reducing *Campylobacter* colonization. These vaccines must be administered via a parenteral route prohibiting mass administration and making them economically not feasible [167,174,175]

3.5.1.4. DNA and mRNA Vaccines

Genetic vaccines represent a significant advancement in the field of vaccinology [176–178]. These vaccines do not require live vector for delivery; they use host-cell mechanisms to produce antigens. Genetic vaccines primarily consist of DNA or mRNA, which is taken up by cells and translated into proteins [179]. Recently, various DNA vaccines, including flagellin-based, outer-membrane protein-based, and prime-boost DNA vaccines, have been investigated for *Campylobacter* control with promising results [180–182]. DNA and mRNA vaccines are generally safer to administer because they do not involve the risks associated with live pathogens [178,183]. They are capable of eliciting both humoral and cellular immune responses, even in the presence of maternal antibodies [184,185]. Although genetic vaccines show a high rate of success, optimizing delivery and ensuring efficient cellular uptake are critical to their overall effectiveness. The delivery of mRNA vaccines via lipid nanoparticles and their storage must be refined, as current methods are not cost-effective for mass immunization [186,187].

3.5.2. Challenges in Campylobacter Vaccine Development

3.5.2.1. Campylobacter Properties

Pan-genome analyses of *Campylobacter* revealed extensive genomic variability, highlighting its highly diverse nature at the genome level [188–191]. This significant genetic diversity indicates that a vaccine targeting only one or a few strains may not be effective against many circulating *Campylobacter* strains in the field. Adding to this challenge is the phase variation phenomenon, which allows bacteria to swiftly adapt to their new surroundings and effectively colonize and survive in the phase of host immune response [192–194]. Through phase variation, bacteria can generate new subpopulations with distinct phenotypes without undergoing overall changes in their genetic content [194–196]. In *Campylobacter*, more than 30 genes, including those encoding key cell surface components, such as lipooligosaccharides, capsular polysaccharides, and flagellin, are differentially regulated in response to the external environment. This phase variation leads to the expression of different versions of surface antigens, which can make vaccines ineffective since the immune response produced by the vaccine may no longer recognize the altered antigens. Consequently, polymorphism arising from phase variation presents a challenge for the development of a single vaccine that is effective against all relevant bacterial forms. Even the vaccines that initially provide protective immunity may eventually lose their effectiveness as the bacterial population dynamically changes its antigen profile [197,198].

3.5.2.2. Host Factors Influencing Vaccinal Immunity

One of the major hurdles in *Campylobacter* vaccine development is the poor understanding of Campylobacter infection immunobiology [159]. Typically, newly hatched chicks are *Campylobacter*-free, and maternal antibodies provide initial protection by delaying the start of colonization [199–202]. Vaccination of breeder hens with bacterin and subunit vaccines resulted in chicks possessing anti-*Campylobacter* antibodies in their blood and mucus, offering some protection, although this protection waned after approximately two weeks [203,204]. Notably, *Campylobacter* colonization usually begins at around three weeks of age, a timeframe that coincides with a decrease in maternal antibody levels [204–206]. In addition to this complexity, mucosal immune system of chicks does not fully mature until around seven weeks, which is after the typical six-week market age for broilers [24,25,207]. This delayed immune maturation is further supported by studies on antibody-associated clearance in bursectomized birds, which indicate that adaptive immune responses develop after

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approximately six weeks, suggesting that achieving effective immune-based protection is more feasible in older, adult birds [199,208–211].

The mucous layers of the lower digestive tract are colonized by *Campylobacter* without provoking any notable immune response [212]. In contrast, effective vaccines elicit a strong intestinal mucosal immunity to combat *Campylobacter* colonization and infection (163, 209). Most injectable vaccines do not produce adequate immunity because *Campylobacter* remains in the intestinal lumen and does not trigger a serious infection to elicit mucosal immune responses. Also, the anatomical features of the chicken immune system present several obstacles. Unlike mammals, chickens lack lymph nodes, which play a key role in antigen presentation and initiation of adaptive immune responses. As a result, secondary lymphoid tissues contribute significantly to the immunity provided by vaccination [214,215]. The Bursa of Fabricius is a specialized lymphoid organ critical for the development of B cells and production of antibodies; however, it undergoes regression with age [216]. Therefore, effective vaccines targeting gut-associated lymphoid tissues (GLAT) and stimulating local mucosal immunity are required for *Campylobacter* control [217,218].

3.5.2.3. Administration and Management of Vaccines

Although small-scale laboratory experiments have shown success, *Campylobacter* vaccines do not yield the same effectiveness under field conditions. The diverse nature of poultry rearing systems, spanning from small-scale backyard operations to large-scale commercial enterprises, presents a significant challenge for the implementation of a standardized and universally effective vaccination protocol [67]. In controlled laboratory settings, each bird receives a precisely measured vaccination dose, which is impractical in the field settings. To enable practical and cost-effective scaling up for larger flocks, mass vaccine administration techniques such as in ovo, water, or spray application systems are employed. These techniques often result in irregular immune responses and varying rates of vaccine uptake [219].

3.5.3. Success Stories and Promising Campylobacter Vaccine Candidates

Despite the unavailability of a commercial *Campylobacter* vaccine for poultry, several studies have demonstrated significant reductions in *Campylobacter* colonization in the chicken intestines. These promising results offer hope for optimizing and developing scalable vaccination strategies in the future. Although, the main focus of this review is on vaccine studies that have reported substantial and statistically significant reductions in *Campylobacter* colonization, Table 1 presents an overview of all poultry *Campylobacter* vaccine studies to date.

3.5.3.1. Autogenous Vaccines

A whole-cell autogenous vaccine targeting *Campylobacter* genes essential for extraintestinal survival was created using a genomic tailoring approach. The progeny of broiler breeders that received the vaccine showed a nearly 50% decrease in *Campylobacter* isolates that colonized and carried extraintestinal survival genes, as well as a notable decrease in meat surface survival. A logistic regression model estimated that the vaccine could successfully target 65% of the population of clinically relevant *Campylobacter* strains. This vaccine strategy is an effective method for combating bacterial infections by targeting bacterial lineages linked to infection and transmission risk within a larger commensal population [220].

3.5.3.2. Subunit Vaccines

Subcutaneous administration of 125 μg of the outer membrane (OMP) fraction of *C. jejuni* resulted in significantly lower *Campylobacter* levels in the cecal contents compared to the oral route of administration. When these outer membrane components were delivered subcutaneously via nanoparticles, *Campylobacter* was undetectable. However, 13% of the chickens showed detectable levels of *Campylobacter* in the intestines when non-encapsulated outer membrane components were

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administered subcutaneously. The serum IgA (IgG) and IgY responses appeared earlier and were higher in the groups that received the vaccine subcutaneously with nanoparticle encapsulated OMP vaccine showing higher IgY and IgA titers in cloacal feces than the other OMP vaccine types. These findings indicate that subcutaneous delivery of OMPs, both with and without nanoparticle encapsulation, effectively stimulated antibody production and significantly reduced *Campylobacter* colonization in the intestine [221]. Similarly, vaccination with chitosan/pCAGGS-*flaA* nanoparticles intranasally reduced the bacterial colonization by 2-3 $\log_{10}$ [222]. Furthermore, vaccination with recombinant peptides derived from CadF, FlaA, and a combined CadF-FlaA-FlpA protein of *C. jejuni* significantly lowered *Campylobacter* loads in the ceca, with median $\log_{10}$ reductions of 3.35 for CadF, 3.11 for FlaA, and 3.16 for the fusion protein [163].

3.5.3.3. Live Attenuated Vaccines

Vaccinating chickens with a modified *Salmonella* strain expressing the *cjaA* gene from *C. jejuni* stimulated the production of IgY and IgA antibodies against the outer surfaces of both *Salmonella* and *Campylobacter*. In contrast to the control group, in which all chickens were heavily colonized, only 15% of the vaccinated chickens had high levels of *Campylobacter* (above 10^3 CFU/g) in their ceca [223]. Similarly, a *Salmonella* strain carrying the *dps* gene of *C. jejuni* demonstrated a 2.5 log reduction in *Campylobacter* levels following experimental infection [224]. Oral delivery of an *E. coli* strain that produces *C. jejuni* N-glycan resulted in 65% protection against *Campylobacter* colonization, whereas all unvaccinated chickens became colonized. Combining the N-glycan vaccine with the probiotics *A. mobilis* or *L. reuteri* enhanced weight gain, IgY antibody production, and overall effectiveness of the vaccination [166].

3.5.3.4. DNA Vaccine

Four novel vaccine candidates discovered using reverse vaccination technology demonstrated a significant decrease in the cecal burden of *Campylobacter* in Ross broiler chickens. These findings indicated a notable drop in the *Campylobacter* load by 4.2 log10 CFU/g, which could potentially reduce the risk of human campylobacteriosis by 76–100%. However, these findings proved challenging to reproduce consistently, necessitating further investigation to develop a reliable vaccine [42,225–227].

Table 1. Summary of the vaccine approaches investigated for poultry *Campylobacter*.

Vaccine	Chicken breed (chicken type)	Age at Vaccination	Vaccination regimen	Challenge		Reduction in levels (mean log10 CFU/gram) of *Campylobacter*	Reference
				Age	Strain (dose)		
Live attenuated *Salmonella* vaccine expressing CfrA or CmeC proteins	Cornish x Rock (broiler)	Day 7	Oral administration of 200 µl of *Salmonella* (1×10^9 CFU/ml) expressing CfrA or CmeC	Day 28	*C. jejuni* NCTC 11168 (2×10^3 CFU/bird)	No significant reduction	[160]
Nanoparticle-encapsulated OMPs of *C. jejuni* 81–176	Not specified	Day 7 and Day 21	Oral administration of 25 or 125 µg of nanoparticle-encapsulated OMPs or OMPs alone Subcutaneous administration of 25 or 125 µg of nanoparticle-encapsulated	Day 35	*C. jejuni* 81–176 (2×10^7 CFU/bird)	No significant reduction	[221]

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			OMPs or OMPs alone				
Live *Salmonella* Typhimurium *ΔaroA* strain expressing CjaA of *C. jejuni*	Light Sussex (broiler)	Day 1 and Day 14	Oral gavage of 0.3 ml of stationary phase culture (1×10^8 CFU/ml)	Day 28	*C. jejuni* M1 (1×10^7 CFU/bird)	Significant 1.4 $\log_{10}$ CFU/g reduction	[211]
Purified recombinant CjaA	Light Sussex chickens (broiler)	Day 1 and Day 15, or Day 15 and Day 29	Subcutaneous administration of 14 μg of rCjaA with TiterMax adjuvant	Day 29/Day 44		No significant reduction	
Autogenous poultry vaccine	Ross (broiler)	14 and 18 weeks of age	Intramuscular administration of 0.5 ml of oil-based autogenous vaccine	Not a challenge study	Measured natural colonization	No significant reduction	[220]
FliD and FspA	White Leghorn (layer)	Day 1 and Day 14	Subcutaneous administration of 4.3×10^{10} moles of each recombinant protein, FliD and FspA, with TiterMax Gold adjuvant	Day 28	*C. jejuni* M1 (1×10^7 CFU/bird)	2 $\log_{10}$ CFU/g in reduction with FliD (statistically significant)	[228]
Eimeria tenella-expressing CjaA	White Leghorn (layer)	Group 1: Day 1 Group 2: 1/3/7/20	Oral administration of 100, 500, 3000, and 5000 fourth-generation *CjaA*-transfected parasites	Day 28	*C. jejuni* 02M6380 (1×10^5 CFU/bird)	One order reduction (statistically significant)	[229]
FlpA with ten N-heptasaccharide glycan Moieties	White Leghorn (layer)	Day 0 and Day 14	Subcutaneous administration of 100 μg of FlpA with TiterMax Gold or the molar equivalent of FlpA-10×GT in 100 μl	Day 28	*C. jejuni* NCTC11168H (1×10^5 CFU/bird)	No significant reduction	[230]
Ent–KLH conjugate vaccine	White Leghorn (layer)	Day 7, Day 21, and Day 35	Intramuscular administration of 100 μg of Ent–KLH conjugate vaccine with Montanide adjuvant	Day 49	*C. jejuni* (1×10^4 CFU/bird)	3-4 $\log_{10}$ unit reduction in the cecum (statistically significant)	[231]
	White Leghorn (layer)	Day 7 and Day 21	Intramuscular administration of 100 μg of Ent–KLH conjugate vaccine with Montanide adjuvant	Day 35	*C. jejuni* (1×10^4 CFU/bird)	3-4 $\log_{10}$ unit reduction in the cecum (statistically significant)	
Recombinant YP437 protein	Ross 308 (broiler)	Day 5 and Day 12	Intramuscular administration of 100 μg of recombinant YP437 protein (YP437 I2, P I2, YP437 I4, and P I4) emulsified with adjuvant MONTANIDETM ISA 78 VG	Day 19	*C. jejuni* (1×10^4 CFU/bird)	No significant reduction	[232]

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Plasmid DNA prime/recombinant protein boost vaccination (YP437 and YP9817)	Ross 308 (broiler)	Day 12	Intramuscular administration of 100 µg of recombinant protein emulsified in MONTANIDE™ ISA 78 VG	Day 19	*C. jejuni* C97Anses 640 (1×10^4 CFU/bird)	No significant reduction	[181]
	Ross 308 (broiler)	Day 5	Intramuscular administration of 50 µg of plasmid DNA				
Lactococcus lactis expressing JlpA	Vencobb (broiler)	Day 7	Oral gavage of $1x10^9$ CFU /100 µl of *Lactococcus lactis* expressing recombinant JlpA	Day 28	*C. jejuni* isolate BCH71 (1×10^8 CFU/bird)	No significant reduction	[233]
			Subcutaneous administration of 50 µg of recombinant JlpA emulsified in incomplete Freund's adjuvant				
Bacterin vaccine (Mix of 13 *Campylobacter* suspensions)	Ross 308 (broiler)	28, 30, 32, and 34 weeks	Intramuscular administration of 8.1 log10 CFU inactivated *Campylobacter* (7 $\log_{10}$ CFU/*Campylobacter* strain)	Day 7 Day 14 Day 21	*C. jejuni* strain KC40 ($10^{2.5}$ and $10^{3.5}$ CFU/bird)	No significant reduction	[203]
Subunit vaccine (6 immunodominant *Campylobacter* antigens)	Ross 308 (broiler)		Intramuscular administration of 75 µg of protein with Freund's complete and incomplete adjuvant				
Diphtheria toxoid *C. jejuni* capsular polysaccharide- vaccine (CPSconj)	Ross 308 (broiler)	Day 7 and Day 21	Subcutaneous administration of 25 µg of CPSconj with 10 µg CpG or 100 µl Addavax adjuvant	Day 29	*C. jejuni* 81-176 (2×10^7 CFU/bird)	0.64 $\log_{10}$ reduction (statistically significant)	[234]
Chitosan/pCAGGS-flaA nanoparticles	White Leghorn (layer)	Day 1, Day 15, and Day 29	Intranasal administration of 150 µg chitosan/pCAGGS -*fla*A nanoparticles	Day 42	*C. jejuni* ALM-80 (5×10^7 CFU/bird)	2 $\log_{10}$ in the cecum (statistically significant)	[222]
LT-B/fla *hybrid* protein	Breed not specified (broiler)	Day 7 and Day 21	Oral administration of 250 µg, 500 µg, 750 µg, and 1mg of LT-B/fla *hybrid* protein; intramuscular administration of 250µg, and 1 mg of LT-B/Fla *hybrid* protein	Day 28	*C. jejuni* A74 ($2x10^8$ CFU/bird)	Statistically significant reduction of the number of *Campylobacter* positive birds	[213]
CjaA, CjaD, and hybrid protein rCjaAD of *C. jejuni*	Hy-line (layer)	Day 1, Day 9, and Day 19	Oral or subcutaneous administration of 2.5×10^9 CFU of *L. salivarius* GEM particles with	Day 30	*C. jejuni* 12/2 ($1x10^4$ CFU/bird)	No significant reduction	[213]

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			CjaALysM and CjaDLysM				
	Rosa 1 (broiler)	18-day-old embryo	In ovo administration of 0.1 ml of inoculum rCjaAD with GRMs particles or liposomes into the amniotic fluid	Day 14	*C. jejuni* 12/2 ($1x10^6$ CFU/bird)	Statistically significant reduction of cecal loads of *Campylobacter*	
Live attenuated *Salmonella* Typhimurium strain expressing *C. jejuni* CjaA	Cobb 500 (broiler)	Day 1 and Day 14	Oral administration of ~10^8 CFU of *S.* Typhimurium strain χ9718 harboring pUWM1161 (Asd^+ vector carrying the *cjaA* gene)	Day 28	*C. jejuni* Wr1 ($1x10^5$ CFU/bird)	No significant reduction	[235]
Live attenuated *Salmonella* expressing linear peptides of *C. jejuni* (Cj0113, Cj0982c, and Cj0420)	Cobb-500 (broiler)	Day 1	Oral gavage of 10^8 CFU/ml *Salmonella*	Day 21	*C. jejuni* PHLCJ1-J3 ($2.5×10^6$ CFU/bird)	4.8-log reduction in the ileum with Cj0113 (statistically significant)	[210]
Live attenuated *Salmonella* expressing linear peptides of *C. jejuni* (Cj0113)			Oral gavage of 10^8 CFU/ml *Salmonella* 10^8 CFU/ml			4-log reduction - undetectable level in the ileum with Cj0113 (statistically significant)	
CmeC and CfrA	Cobb 500 (broiler)	18-day-old embryo	In ovo administration of 50 µg pCmeC-K or 50 µg pCfrA into the amniotic fluid	Day 14	*C. jejuni* NCTC 11168 ($5×10^7$ CFU/bird)	No significant reduction	[180]
			In ovo administration of DNA vaccines emulsified with incomplete Freund's adjuvant	Day 21		No significant reduction	
pcDNA3-YP DNA vaccines YP_001000437.1, YP_001000562.1, YP_999817.1, and YP_999838.1	Ross PM3 (broiler)	Day 5 and Day 12	Intramuscular administration of with 300 µg of pcDNA3-YP, supplemented with 50 µg of unmethylated CpG ODN2007 followed by intramuscular administration of 100 µg of recombinant proteins emulsified in MONTANIDE™ ISA70 VG	Day 19	*C. jejuni* C97Anses 640 ($1×10^5$ CFU/bird)	2.03, 3.61, 4.27 and 2.08 log 10 reductions of P562, YP437, YP9817 and P9838 groups, respectively (statistically significant)	[226]
			Intramuscular administration of with 300 µg of pcDNA3-YP9817, supplemented with 50 µg of			No significant reduction	

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			unmethylated CpG ODN2007 followed by intramuscular administration of 100 µg of recombinant proteins emulsified in MONTANIDE™ ISA70 VG				
CmeC	Breed not specified (broiler)	Day 7 and Day 21	Oral gavage with 50 or 200 µg of CmeC vaccine with or without with 10 µg of mLT	Day 35	*C. jejuni* NCTC 11168 (1×10^6 CFU/bird)	No significant reduction	[236]
	White Leghorn chickens (layer)	Day 21 and Day 35	Oral and subcutaneous administration of 50 or 200 µg of CmeC vaccine with or without 70 µg of mLT	Day 49	*C. jejuni* NCTC 11168 (1×10^5 CFU/bird)	No significant reduction	
Lactococcus lactis NZ3900/pNZ8149 expressing cjaA	White leghorn (layer)	Day 5 to 11, and Day 19 to 25	Oral administration of 2×10^{10} CFU of *L. lactis* NZ3900-sCjaA-Ltb, NZ3900-sCjaA, NZ3900-pNZ8149s, and NZ3900-pNZ8149	Day 33	*C. jejuni* NCTC 11168 (1.5×10^6 CFU/bird)	2.35 $\log_{10}$ and 2.05 $\log_{10}$ reduction with NZ3900-sCjaA vaccine group at post 5 DPI (statistically significant)	[162]
Glycoproteins of FlpA and SodB	White Leghorn (layer)	Day 6 and Day 16	Intramuscular administration of 240 µg of FlpA and G-FlpA or 138 µg of SodB and G-SodB.	Day 20	*C. jejuni* M1 (1×10^7 CFU/bird)	No significant reduction	[237]
					C. jejuni M1 (10^2 CFU/bird)	No significant reduction	
Glycoprotein G-ExoA	White Leghorn (layer)	Day 6 and Day 16	Intramuscular administration of 95 µg protein of ExoA or G-ExoA with MontanideTM ISA 70 VG adjuvant	Day 20	*C. jejuni* M1 (1×10^2 CFU/bird)	Reduction on Day 37 with ExoA-vaccinated group (statistically significant)	[238]
					C. jejuni 11168H. *C. jejuni* M1 (1×10^4 CFU/bird)	Reduction on Day 37 with ExoA and G-ExoA-vaccinated groups (statistically significant)	
Bacterin and subunit vaccine	Ross 308 (broiler)	18-day-old embryo	In ovo administration of 7.4 log10 CFU inactivated *Campylobacter*/bacterin dose of bacterin vaccine injected into the amniotic cavity	Day 19	*C. jejuni* KC4 (1×10^7 CFU/bird)	No significant reduction	[239]
			In ovo administration of 28.5 µg of 6 immunodominant				

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			Campylobacter antigens with ESSAI IMS 1505101OVO1 adjuvant				
C. jejuni Dps	Cornish × Rock (broiler)	Day 10 and Day 24	Subcutaneous administration of 0.2 mg recombinant Dps protein with Freund's complete adjuvant	Day 34	*C. jejuni* NCTC11168 (1×10^5 CFU/bird)	No reduction	[224]
		Day 3, Day 10, and Day 16	Oral gavage of *Salmonella* Typhimurium strain χ9088 expressing *C. jejuni* Dps in 0.5 ml	Day 26		2.92 $\log_{10}$ reduction (statistically significant)	
PLGA-encapsulated CpG ODN	Breed is not specified (layer)	Day 14	Oral administration of 5 μg or 50 μg of soluble CpG	Day 15	*C. jejuni* (10^7 CFU/bird)	1.23 and 1.32 log reduction at 8-day post infection with low and high dose, respectively (statistically significant)	[240]
	Breed is not specified (layer)		Oral administration of 5 μg E-CpG			0.9, 1.9 and 1.89 log reduction at 8, 15 and 22 days of post-infection (statistically significant)	
	Breed is not specified (layer)		Oral administration with a high dose of E-CpG (25 μg)			1.46 log10 reduction at day 22 post-infection (statistically significant)	
	Breed is not specified (broiler)		Oral administration of a low dose of *C. jejuni* lysate (4.3 μg protein)			2.14 and 2.14 log10 at day 8 and day 22 post-infection, respectively (statistically significant)	
	Breed is not specified (broiler)		Oral administration of combination of E-CpG ODN (25 μg) and *C.* Oral administration of a combination of E-CpG ODN (25 μg) and *C. jejuni* lysate (4.3 μg protein)			2.42 log10 at day 22 post-infection (statistically significant)	
C. jejuni Type VI secretion system (T6SS) protein Hcp	Vencobb (broiler)	Day 7, Day 14, and Day 21	Oral gavage of 50 μg rhcp loaded CS-TPP NPs (CS-TPP-Hcp)	Day 28	*C. jejuni* isolate BCH71 (1×10^8 CFU/bird)	1 log reduction (statistically significant)	[241]
			Subcutaneous administration of 50 μg of rhcp emulsified with			0.5 log reduction (statistically significant)	

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			Incomplete Freund's adjuvant				
Recombinant NHC flagellin	Ross 308 (broiler)	18.5-day-old embryo	In ovo administration of 40 or 20 µg NHC flagellar protein with 10 mM Tris (pH 9.0), 20% glycerol, 5 mM sucrose	day 18	*C. jejuni* (1×10^5 CFU/bird)	No significant reduction	[242]
Recombinant *C. jejuni* peptides of CadF, FlaA, FlpA, CmeC, and CadF-FlaA-FlpA fusion protein	Cornish cross (broiler)	Day 6 and Day 16	Intramuscular administration of 240 µg of GST-tagged 90 mer peptides or equal mixure of CadF-His, FlaA-His, and FlpA-His (trifecta group) emulsified in Montanide ISA 70 VG	Day 20	*C. jejuni* (2×10^8 CFU/bird)	3.1, 3.3, 3.1, and 1.7 log reductions observed with Trifecta, FlpA, FlaA and CadF, respectively (statistically significant)	[163]

CfrA: ferric enterobactin receptor), CjaA: C. jejuni aminoacid binding protein, CjaD: peptidoglycan-binding protein, CmeC: an essential component of CmeABC multidrug efflux pump, CpG ODN: oligodeoxynucleotides containing unmethylated CpG motifs, CS-TPP NPs: Chitosan-Sodium tripolyphosphate nanoparticles, DPI: days post infection, Dps: DNA binding protein, Ent–KLH conjugate vaccine: Enterobactin conjugated to the carrier keyhole limpet hemocyanin, FlaA: Flagellin A, FliD: flagellum-capping protein, FlpA-10×GT : FlpA with 10 N-Heptasaccharide Glycan Moieties, FspA: flagellum-secreted protein, GEM particles: Gram-positive Enhancer Matrix particles, JlpA: *C. jejuni* lipoprotein A, LT-B: Binding subunit of the heat-labile enterotoxin, mLT: modified *E. coli* heat-labile enterotoxin, ODN: oligodeoxynucleotides, OMPs: outer membrane proteins, and SodB: superoxide dismutase.

4. Conclusion and Future Perspectives of Campylobacter Control:

As a food-borne pathogen, *Campylobacter* continues to pose a challenge to global public health, with poultry serving as the primary source of human infection. Growing concerns regarding antimicrobial resistance and the push for antibiotic-free poultry production have accelerated the urgency for sustainable and long-term control measures against *Campylobacter* in poultry. This comprehensive review focuses on the possible preharvest options to control *Campylobacter* colonization in chickens, with a special emphasis on vaccination. Because a single strategy cannot completely prevent *Campylobacter* colonization, our review highlights the importance of a multifaceted approach that integrates several on-farm interventions. Strict biosecurity measures play a fundamental role in preventing the introduction and spread of *Campylobacter*. Additionally, dietary interventions such as probiotics, prebiotics, postbiotics and feed additives offer promising avenues for modulating the gut microbiome and enhancing host resistance to *Campylobacter* colonization. Importantly, vaccination stands out as one of the most logical approaches for preventing and reducing *Campylobacter* colonization at the source level. Although there is currently no commercial vaccine available, ongoing research on multi-epitope and universal vaccine designs coupled with advancements in delivery systems and formulations, offers great promise in addressing the challenges presented by the genetic diversity of the pathogen and the unique immunological characteristics of poultry.

4.1. Future Prospects:

4.1.1. Biosecurity Enhancing Innovations

Biosecurity innovations provide a more efficient primary protective barrier against the entry of *Campylobacter* into poultry farms [244]. Improved fly control management through biological traps

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and insecticide-impregnated netting has significantly reduced the prevalence of *Campylobacter* on farms. Furthermore, managing the poultry house environment using new technologies such as electrostatic air filtration, UV-based disinfection, automated cleaning system and water purification system offers promising tools for reducing environmental exposure to *Campylobacte*r. More advanced features like **real-time monitoring systems** for detecting contamination hotspots on farms enable early action against *Campylobacter* and preventing its entry and spread [245]. However, effective implementation depends on human compliance, including proper training and stringent adherence to biosecurity protocols by farm staff [246,247].

4.1.2. Studies Targeting Campylobacter and Host Interactions

Inadequate knowledge of *Campylobacter* pathophysiology and host reactions is one of the main challenges in controlling these bacteria [57]. The primary goal of ongoing research is to identify virulent genes, including colonization factors, and metabolic adaptations necessary for developing rational mitigation strategies. Studying avian innate and adaptive immunity against *Campylobacter* and host resistance indicators that can prevent *Campylobacter* colonization is crucial for maintaining a balance where *Campylobacter* colonization occurs without causing invasive infection [248–250]. Advanced multi-omics research is expected to make these investigations conceivable [251–254].

4.1.3. Genetic Selection of Campylobacter-Resistant Breeds

A long-term approach to control *Campylobacter* involves genetic selection of breeds resistant to bacterial colonization. Research has demonstrated that the Quantitative Trait Loci (QTL), major histocompatibility complex (MHC), and immune response genes vary among birds with various levels of resistance to *Campylobacter* (240, 241). The selection of breeder stocks resistant to *Campylobacter* can help to control colonization at the primary production level.

4.1.4. Developing Effective Vaccination Strategies

One of the main challenges in developing an effective *Campylobacter* vaccine is the high antigenic diversity among strains, hindering cross-protection. This issue can be addressed by identifying the conserved and protective antigens shared between multiple strains [257]. Further research is needed to identify broad-spectrum vaccine targets (e.g., multi-epitope vaccines) through the use of in silico prediction tools. Reverse vaccine technology offers avenues to identify vaccine antigen candidates that offer protection against a wide range of *Campylobacter* strains [258,259]. Additionally, optimization of mucosal vaccine delivery systems can enhance vaccine efficacy against *Campylobacter* colonization [242,260].

4.1.5. Microbiota Targeting Interventions

A healthy gut microbiota can inhibit *Campylobacter* colonization through competitive exclusion and the production of antimicrobial metabolites (e.g., short-chain fatty acids) thereby improving mucosal immunity. These beneficial effects can be achieved through the use of prebiotics, probiotics and postbiotics, which help modulate the gut microbiota and support protective microbial communities [261,262]. Emerging technologies like fecal microbiota transplantation (FMT) and precision microbiome engineering are still in the early stages but represent promising future avenues for C*ampylobacter* control [117,263].

4.1.6. Cross-Sectoral Collaboratory Efforts (One Health)

Effective preharvest control strategies require strong and sustained collaboration among researchers, poultry industry, and policymakers. Success depends on teamwork, planning in advance, and a combination of efforts across all three sectors. Future control depends on teamwork, proactive planning, and a coordinated effort across all the three sectors. The adoption of the One

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Health approach, combined with the practical application of scientific innovations at the farm-level can significantly greatly reduce the global burden of *Campylobacter* [264–266].

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Abbreviations

The following abbreviations are used in this manuscript:

AMR	Antimicrobial resistance
CFU	Colony forming units
EOs	Essential oils
FMT	Fecal microbiota transplantation
FOS	Fructooligosaccharides
GBS	Guillain-Barré Syndrome
GIT	Gastrointestinal tract
GLAT	Gut-associated lymphoid tissue
GOS	Galactooligosaccharides
IBS	Irritable bowel syndrome
IMO	Isomalto-oligosaccharides
MHC	Major histocompatibility complex
PPE	Personal protective equipment
QTL	Quantitative Trait Loci
VBNC	Viable but non-culturable state

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