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Critical Review—

Campylobacter in Poultry: Ecology and Potential Interventions

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SUMMARY. Avian hosts constitute a natural reservoir for thermophilic *Campylobacter* species, primarily *Campylobacter jejuni* and *Campylobacter coli*, and poultry flocks are frequently colonized in the intestinal tract with high numbers of the organisms. Prevalence rates in poultry, especially in slaughter-age broiler flocks, could reach as high as 100% on some farms. Despite the extensive colonization, *Campylobacter* is essentially a commensal in birds, although limited evidence has implicated the organism as a poultry pathogen. Although *Campylobacter* is insignificant for poultry health, it is a leading cause of food-borne gastroenteritis in humans worldwide, and contaminated poultry meat is recognized as the main source for human exposure. Therefore, considerable research efforts have been devoted to the development of interventions to diminish *Campylobacter* contamination in poultry, with the intention to reduce the burden of food-borne illnesses. During the past decade, significant advance has been made in understanding *Campylobacter* in poultry. This review summarizes the current knowledge with an emphasis on ecology, antibiotic resistance, and potential pre- and postharvest interventions.

RESUMEN. *Revisión crítica - Campylobacter* en la avicultura: Ecología y posibles medidas de control.

Los hospederos aviares constituyen un reservorio natural para las especies termófilas de *Campylobacter*, principalmente *Campylobacter jejuni* y *Campylobacter coli* y con frecuencia las parvadas avícolas son colonizadas en el tracto intestinal con un alto número de organismos. Las tasas de prevalencia en las aves comerciales, especialmente en las parvadas de pollo de engorde a la edad de procesamiento, pueden llegar a ser tan altas como el 100% en algunas granjas. A pesar de su extensa colonización, *Campylobacter* es esencialmente un comensal en las aves, aunque evidencia limitada ha implicado a este organismo como un patógeno en las aves comerciales. Aunque *Campylobacter* no representa un problema importante de salud en las aves comerciales, es la principal causa de gastroenteritis de origen alimentario en los seres humanos en todo el mundo y la carne de pollo contaminada es reconocida como la principal fuente de exposición para los humanos. Por lo tanto, se han dedicado considerables esfuerzos de investigación al desarrollo de medidas para disminuir la contaminación por *Campylobacter* en las aves comerciales, con la intención de reducir la presentación de esta enfermedad transmitida por los alimentos. Durante la década pasada, se ha logrado un avance significativo en el conocimiento sobre *Campylobacter* en las aves comerciales. Esta revisión resume los conocimientos actuales, con énfasis en la ecología, la resistencia a los antibióticos, y las potenciales medidas de control antes y después del procesamiento.

Key words: *Campylobacter*, poultry, broiler, colonization, carcass contamination, control measures

Abbreviations: AMPs = antimicrobial peptides; CFU = colony-forming units; EU = European Union; FDA = United States Food and Drug Administration; FSIS-USDA = Food and Safety Inspection Service-United States Department of Agriculture; NARMS = National Antimicrobial Resistance Monitoring System

Domestic poultry (e.g., chickens, turkeys, ducks, and geese) and wild birds are frequently infected with thermophilic *Campylobacter*, primarily *Campylobacter jejuni* and *Campylobacter coli* (95,207,214, 226,269). *Campylobacter* prevalence rates, especially in slaughter-age conventional broiler flocks, could reach as high as 100% on some farms worldwide. Both *C. jejuni* and *C. coli* are well adapted to the avian host and reside mainly in the intestinal tract of birds. Despite extensive colonization in the intestine (up to 10^9 colony-forming units [CFU]/g cecal contents), *Campylobacter* infections in general produce little or no overt disease in avian host (55,113,152, 182,251). However, limited data suggest that *Campylobacter* colonization may be associated with disease production in poultry under certain conditions. For example, a very-recent study reported the production of intestinal inflammation and diarrhea in fast-growing breeds of broiler chickens following experimental challenge (126). Also, vibrionic hepatitis with high morbidity and mortality associated with *Campylobacter* infection was reported in laying hens and ostriches, (36,225); however, it was questionable if *Campylobacter* alone was sufficient to cause this condition as other predisposing factors may be required for the induction of the disease (135). Some recent investigations also suggested that *Campylobacter* colonization in chickens was negatively associated with intestinal function and growth performance as well as with bird welfare (16,259).

Extensive research on *Campylobacter* on poultry farms has been undertaken over the last two decades, the majority of which were on commercial broiler production in developed countries. As a result, new and significant knowledge has been gained regarding the epidemiology and ecology of *Campylobacter* in poultry. However, many gaps remain and effective intervention strategies for the control of *Campylobacter* are still lacking. Several distinct features of *Campylobacter* in poultry have been discovered. First, *Campylobacter* is rarely detected in young birds less than 2–3 wk of age under commercial production conditions (10,82,182,185,195,209), and

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maternal antibodies seem partially responsible for protection (45,206,209). Once a broiler flock is infected with *Campylobacter*, the majority of the birds within the flock become colonized within a short time period (20,25,43,97,228). Second, although the overall prevalence of *Campylobacter* in poultry is high, there is considerable variation in the prevalence at the farm and flock levels (2,35,43,82,195,203,228). Third, vertical transmission via eggs does not play a major role in the transmission of *Campylobacter* on poultry farms. Epidemiologic studies from around the world have clearly indicated that horizontal transmission from the environment is the main source of *Campylobacter* colonization in poultry and that vertical transmission from breeder flocks to broilers is insignificant (20,41,182,185,205,207,222,262). Potential sources of flock infection include old litter, untreated drinking water, other farm animals, domestic pets, wildlife species, flies, insects, farm equipment and transport vehicles, and farm workers. The lack of evidence for vertical transmission distinguishes *Campylobacter* from *Salmonella*, which can be transmitted via eggs.

Despite its commensal nature in poultry, *Campylobacter* is among the leading bacterial zoonotic pathogens of importance to food safety and public health, with *C. jejuni* being responsible for the majority of human Campylobacteriosis, followed by *Campylobacter coli* and rarely by *Campylobacter lari* and others. The poultry reservoir, especially broiler meat, is recognized as the most-important vehicle for *Campylobacter* transmission to humans (95,170,217,249). In the United States, a recent study ranked *Campylobacter* in poultry as the highest pathogen-food combination with the largest burden on public health considering the number of cases, hospitalization, death, economic cost, and health-related quality of life (21). As reported by the Centers for Disease Control and Prevention (CDC) FoodNet surveillance program in 2013, *Campylobacter* ranked second (13.82 per 100,000 population) only to *Salmonella* (15.19 per 100,000 population) among the causes of laboratory confirmed food-borne illnesses in 10 U.S. states covering approximately 15% of the U.S. population. (60). A recent report estimates that *Campylobacter* is not only among the most-common causes of domestically acquired food-borne illnesses in humans (over 800,000 cases/yr) but also is among the leading causes of hospitalization (over 8,000 annually) in the United States (212). In the European Union (EU), *Campylobacter* is the most-commonly reported bacterial gastroenteritis pathogen with an incidence rate of 55.5 per 100,000 population in 2012 (95).

Most of *Campylobacter*-related illnesses in humans are sporadic and characterized by watery or bloody diarrhea (or both), abdominal cramps, and possible fever; however, severe conditions may occur in immunocompromised patients, requiring antibiotic treatment (84,170). *Campylobacter* infection is also associated with Guillain-Barre syndrome and other postinfectious autoimmune sequelae such as reactive arthritis and irritable bowel syndrome, which may result in serious health consequences (134,146). In addition to the predominant role of chicken meat in sporadic infections, outbreaks due to *Campylobacter* are also commonly associated with consumption of poultry besides raw milk and contaminated surface water (67,84,237,241). Furthermore, the prime impact of poultry in the epidemiology of human Campylobacteriosis is supported by a high prevalence of *Campylobacter* in both live birds and on carcasses and by detection of identical genotypes in both poultry and human infections (100,113,153,175,234,260).

Considering the fact that handling or consumption of contaminated chicken meat is the main risk factor for human Campylobacteriosis, major efforts from various stakeholders have been devoted to finding effective and feasible means of intervention for *Campylobacter* contamination in the poultry production chain. In the United States, the Food Safety and Inspection Service of the Unites States Department of Agriculture (FSIS-USDA) recently (effective since July 2011) established performance standards for *Campylobacter* in poultry slaughter operations (both broilers and turkeys) to reduce carcass contamination in an effort to mitigate the number of human food-borne poisoning cases associated with this pathogen (86,87). The purpose of this review is to provide an overview on the current knowledge of *Campylobacter* in poultry with an emphasis on ecology and potential interventions. It is hoped that the information will facilitate future efforts on developing practical and effective measures to control this important food-borne pathogen.

EPIDEMIOLOGY OF *CAMPYLOBACTER* ON POULTRY FARMS

Prevalence. Many species of poultry, especially commercial chickens and turkeys, frequently carry high levels of *Campylobacter* spp. (primarily *C. jejuni* and *C. coli*) in their intestine as part of the normal microbial flora without showing any signs of clinical disease (55,183,207,226,255). Prevalence of *Campylobacter*-positive poultry flocks are generally high but vary by regions, seasons, and the production types (conventional, free-range, and organic, etc.), with reported *Campylobacter*-positive flocks ranging from 2% to 100% (14,23,55,95,139,141,162,165,182,228,238). It appears that the prevalence of *Campylobacter* is lower in Scandinavian countries than in other European countries, North America, and developing countries. Seasonal variations are observed in the prevalence of *Campylobacter* flocks with a peak in summer and autumn months (20,32,190,228,254). A high prevalence of *Campylobacter* in warm months may be due to an increased fly population and fly-mediated transmission (19,104). There is a general trend that *Campylobacter* is more prevalent in organic and free-range flocks than in conventional production (10,78,116,162,196,248,261). Free access to the outside environments, and longer life span, may account for the increased prevalence rates of *Campylobacter* in organic and free-range productions (269). Similar to these observations, our ongoing longitudinal study (i.e., repeated sampling of multiple flocks on multiple farms for about 2 yr) in a commercial broiler production system in the United States has found a *Campylobacter* prevalence rate of 45% at the flock level and 93% at the farm level (Sahin and Zhang, unpubl. obs.). Interestingly, the ongoing study also revealed substantial variation in *Campylobacter* prevalence, with some houses or farms consistently producing *Campylobacter*-free or *Campylobacter*-positive flocks over multiple production cycles. Detailed epidemiologic investigation of these types of farms and houses with distinct patterns of prevalence may identify tangible risk factors associated with *Campylobacter* presence or absence in poultry flocks which may provide valuable information for implementation of effective on-farm intervention measures.

Colonization and disease. A unique feature of *Campylobacter* ecology in poultry is that the organism is rarely detected in commercial flocks of less than 2–3 wk of age regardless of production types (both conventional and free-range or organic) and species of poultry (both chickens and turkeys) (10,71,113,183,207,228,263). Interestingly, a recent study (141) also found that *Campylobacter* was not detected during the first 3 wk of age in multiple broiler flocks raised on commercial farms with very low biosecurity measures (e.g., presence of multi-age broiler flocks, layer birds, and other livestock with *Campylobacter*-positive

status in the vicinity, huge fly population, incomplete hygiene practices by animal caretakers, etc.) in tropical climates. As also suggested by the authors of this study, the universally observed lag phase in the colonization of poultry by *Campylobacter*, even in the presence of likely exposure to positive birds and other sources, implies that a biologic mechanism of colonization resistance may be present in young birds. Maternal antibodies are widely present in broiler chicks and were shown to be partly responsible for the absence of *Campylobacter* colonization in young chickens (45,206,209). In a broader context, colonization of chickens by *Campylobacter* can be affected by such factors as the age of the bird and strain of the bacterium (46,113,147,206,232). Genotype of the broiler chicken (i.e., growth rate and breed) does not appear to have any significant influence on colonization of birds by *Campylobacter* in field conditions (96,259). Once a broiler flock is infected with *Campylobacter*, the majority of birds become colonized within a few days, and the overall prevalence within the flock reaches the highest level (close to 100% in many cases) at the slaughter age (20,25,43,64,94,228). A recent mathematical model also predicts that *Campylobacter* would impact 95% of a flock of 20,000 birds within 4.4 to 7.2 days after colonization of the first broiler bird (247). Conversely, in poultry with a longer life span (e.g., layer chickens), a decrease in the colonization level by *Campylobacter* may be observed over time as the birds age, and some birds may eventually clear the infection owing to the development of active immunity (1,140,182,206,227).

Birds are naturally infected with *Campylobacter* via the fecal-oral route, after which the organism establishes itself in the intestinal tract with the main site of colonization being the ceca and colon and to a lesser extent the small intestines, liver, and other organs (1,46,65,113,140,174,207). Although young birds may develop clinical disease (e.g., diarrhea and weight loss), as shown in some experimental infections with *Campylobacter* (31,126,148,167, 202,211), the vast majority of studies pointed out the commensal nature of the organism in poultry with no clinical signs of disease production (4,22,145,183,206,227,269). Even in the sporadic events where signs of disease were observed in experimentally infected chicks, gross pathologic and microscopic lesions associated with *Campylobacter* infection were mostly minimal and mainly confined to the gastrointestinal tract (269). A distinct feature of *Campylobacter* colonization in poultry is that the organism resides mainly in the mucus layer of the intestinal crypts, without direct adhesion or invasion of the epithelial cells, producing no signs of overt illness in most cases (22,135,145,156,171,246,265). More recently, it was suggested that *Campylobacter* spp. establish colonization by utilizing a strategy that involves transient invasion of intestinal epithelium to avoid mucosal clearance combined with rapid replication in the intestinal mucus (246). A large number of *Campylobacter* cells (up to 10^9 CFU/g feces) can be recovered in ceca and excreted in feces for a prolonged period (e.g., at least until the slaughter age) following the establishment of organisms in the intestinal tract after both natural and experimental infections (75,113,207). Under the condition of commercial production, chicken flocks can be colonized by single or multiple species and genotypes of *Campylobacter*, even during a single rearing cycle (25,35,75,79,111,119,197,231,261), which has also been reproduced in experimental infections (46). In poultry, especially in broiler chickens, *C. jejuni* is the predominant species colonizing the flocks, followed by *C. coli* and rarely other species; however, *C. coli* has been reported to be the dominant species isolated from commercial turkeys and from organic and free-range chickens (35,116,162,166,197,219,261).

Sources of infection and risk factors for *Campylobacter* colonization. Because newly hatched birds are essentially free of *Campylobacter*, commercial poultry flocks typically start as being *Campylobacter*-negative and usually stay that way until 2–3 wk into the production cycle. As the flocks age, birds eventually become colonized with *Campylobacter*. The organism is ubiquitous in the surrounding farm environment, and the sources of flock infection and risk factors influencing *Campylobacter* introduction are complex in nature. A brief summary of sources and routes of *Campylobacter* introduction into the commercial flocks (primarily intensively reared broiler chickens) is presented below.

A large number of epidemiologic studies conducted in different countries indicated that horizontal transmission from environmental sources is the main route of flock colonization by *Campylobacter* (5,55,113,182,207,230,269). The factors commonly associated with *Campylobacter* colonization in broiler flocks include lack of overall biosecurity on farms, presence of other animals in close proximity to poultry houses (including other poultry species, livestock, pets, and wildlife), age and number of houses on a farm, slaughter age, size of flocks, the practice of partial depopulation (thinning), seasonal and climate changes, use of ventilators, fly population (and lack of fly screens), use of old litter, farm equipment, transport vehicles, and farm workers. Conversely feed, fresh litter, and water are rarely the sources for the initial introduction of *Campylobacter* into poultry flocks, although they can be contaminated by the organism in poultry houses where the birds are colonized and thus can facilitate the spread of *Campylobacter* within production facilities (97,130,157,245,270).

Rodents and flies may act as potential vectors for introduction of *Campylobacter* in poultry houses. Improper rodent control was found to be a risk factor for the occurrence of *Campylobacter* in broiler flocks in some studies (73,188,223,240) but not in others (14,97,137,172). Recent Danish studies have consistently implicated flies as an important risk factor for introduction of *Campylobacter* into broiler flocks (19,104,105,129). It was initially found that large numbers of *Campylobacter*-contaminated flies could enter the chicken houses through the ventilation system in summer months, with *Campylobacter* isolates from the broilers and the flies having the same genotypes (104,105). Recently it was shown that use of fly screens on ventilation openings in chicken houses significantly reduced the number of *Campylobacter*-positive flocks and removed the normal summer peak in *Campylobacter* prevalence (19,106). These findings suggest that flies serve as a vector for transmitting *Campylobacter* on poultry farms, especially during summer when the temperature is high.

Presence of other livestock (including cattle, sheep, and pigs), pets, and fowl other than chickens on poultry farms have been identified as important risk factors for infection of broiler flocks with *Campylobacter* (25,32,73,138,142,223,243,244,245). Although the direction of transmission (from or into the poultry houses) is uncertain in many cases, *Campylobacter*-colonized livestock, in particular cattle, constitute a likely source for flock infection because livestock is a well-known reservoir for *Campylobacter* (72,73,195). Similar genotypes of *Campylobacter*, albeit not always, were isolated from broiler flocks and nearby cattle farms (35,97,181,185,245), suggesting that cattle can be a source of infection for broilers. In a recent, well-designed longitudinal study, it was shown that identical *Campylobacter* genotypes were detected from an adjacent dairy farm prior to their detection from the conventional broiler chicken flocks (195), again suggesting transmission of *Campylobacter* from cattle farms to poultry houses. Furthermore, it was demonstrated in this study that naturally contaminated cattle feces

was a viable source of *Campylobacter* colonization for broiler chickens in a challenge experiment (195).

Farm personnel and equipment can carry *Campylobacter* between broiler flocks or farms and have been found as potential risk factors in some studies (11,25,108,109,185,243). Strict adherence to hygiene by farm workers (such as hand washing, use of separate boots for each house, overall cleanliness of house anterooms, and use and frequency of footbath disinfectant) has been usually associated with a decreased proportion of *Campylobacter*-positive flocks (108,168,243,245). *Campylobacter*-contamination of transport crates, which occurs quite frequently, may be difficult to disinfect effectively, and crates have been shown to carry identical genotypes of the organisms that were recovered from broiler flocks and abattoirs (11,35,107,109,185,228), which suggests that transport crates could contaminate birds during transport to slaughter or they could even introduce *Campylobacter* into the broiler houses.

Recently, *C. jejuni* and *C. coli* were found to be present in 100% and 58.8% of farm litter samples, respectively (93). In laboratory microcosms, *Campylobacter* can survive better in used litter in comparison to new litter (143). The persistence of *Campylobacter* was linked to the availability of nutrients and to the litter's moisture content. Controlled comparisons between chickens raised on reused and new litter showed that, after 1 wk, 60% of chickens from the enclosures containing reused litter were positive for *Campylobacter* while 33% were positive in the enclosures with new litter. Furthermore, at week 6, 63% of chickens in the reused litter enclosures were positive for *Campylobacter*, which was significantly higher than the percentage of *Campylobacter*-positive chickens in enclosures with new litter (143). Collectively, these observations suggest that used litter can act as a reservoir and source for *Campylobacter*, which may be especially important under managements that exploit the same litter for multiple rearing cycles.

All these observations clearly indicate horizontal transmission from the poultry farm environment as the major source of exposure of flocks to *Campylobacter*. Notably, many studies concluded that vertical transmission from breeder flocks via eggs was not a major source in the introduction of *Campylobacter* to broiler houses (20,35,41,185,205), although some controversy still exists (58). Lack of *Campylobacter* colonization during the first weeks of life of broilers, those hatched from eggs originated from breeder flocks infected with *Campylobacter* under natural farms settings, argues against the importance of vertical transmission (20,24,35,41,216, 243,245). Likewise, many studies reported that *Campylobacter* strains infecting broiler flocks and their parent breeder flocks were of different genotypes (3,41,50,185,187,188,245) and thus indicated the unlikelihood of vertical transmission for contamination of poultry flocks with *Campylobacter*. Finally, evidence against the significance of vertical transmission comes from studies in which *Campylobacter* was rarely isolated from eggs or hatchlings (68,118,205,216,221); in only one study reported thus far, hatcheries and young hatchling were shown to be contaminated with live *Campylobacter* (37). The circumstantial evidence for the possible spread of *Campylobacter* by vertical transmission was indicated in several studies in which the organism was isolated from the outer and inner shell surface of eggs laid by *Campylobacter*-positive commercial layers or broiler breeders (68,215,216), from the reproductive tract of hens (34,42,117,131), and from semen of broiler breeder roosters (59). In addition, *Campylobacter* DNA was detected via molecular diagnostics in embryos and newly hatched chicks in several studies (51,52,127).

HOST IMMUNE RESPONSES TO *CAMPYLOBACTER* INFECTIONS IN CHICKENS

Despite the fact that *Campylobacter* colonizes chicken intestine as a commensal, it still triggers immune responses. Generally, *Campylobacter*-induced antibody response is slow and moderate in chickens. The anti-*Campylobacter* serum IgG, IgA, and IgM levels were increased gradually 2–3 wk after experimental inoculation, and mucosal IgA was elevated 3–4 wk upon *Campylobacter* infections in chickens (44,176,257). Laboratory challenge experiments indicated that *Campylobacter*-specific maternal antibodies conferred partial protection against *Campylobacter* colonization in chickens (45,206,209), which demonstrated a protective role of the antibodies in *Campylobacter* infection and provided a rationale for the development of immune intervention strategies to control *Campylobacter* infections in poultry.

Clearly, chicken host immunity to *Campylobacter* infection is different from that to other bacterial infections such as avian salmonellosis (258). Recently, Herman *et al.* (112) comprehensively reviewed chicken intestinal mucosal immune response to *Campylobacter* infection and provided an insightful view on the interaction between *Campylobacter* and the chicken host. It has been suggested (112) that the cecal mucosal crypts, the major colonization site of *Campylobacter*, only develop an inefficient inflammatory response which fails to clear *Campylobacter* from the intestine. In addition, Herman and his colleague (112) proposed the mechanism potentially responsible for the redirection of chicken host immune response toward tolerance, consequently leading to persistent and high-level *Campylobacter* colonization in the chicken gut. Consistent with this theory (112), Connell *et al.* (54) observed that gut-related immune mechanisms are critical for regulating *Campylobacter* colonization levels in chickens. Specifically, mRNA sequence analysis of cecal tissue from 14 *C. jejuni*-susceptible and 14 *C. jejuni*-resistant birds demonstrated that differences in immune response contributed to variation in colonization levels between susceptible and resistant chickens (54). Together, these recent findings have improved our understanding of the delicate interaction between the chicken mucosal immune system and *Campylobacter* infections. Elucidation of the underlying mechanisms for the tolerogenic mucosal immune response may eventually facilitate the development of effective intervention strategies to mitigate *Campylobacter* colonization in poultry.

Although *Campylobacter* primarily colonizes the intestinal tract, it can be isolated from the spleen, liver, and blood in young chickens, suggesting that *Campylobacter* may invade intestinal epithelial cells and become systemic (145,211). It was also demonstrated that *C. jejuni* can breach the gut epithelial barrier, and the *in vitro* invasiveness of *C. jejuni* was correlated with the magnitude of spleen infection in *C. jejuni*-inoculated chickens (40,246). Notably, a recent study by Humphrey and colleagues (126), using four commercial breeds of broiler chickens for experimental infection, found that breed has a significant effect on the outcome of *C. jejuni* infection and the immune response. Specifically, all breeds mounted an innate immune response, but the length and magnitude of inflammatory responses varied in different breeds, leading to commensal colonization in some breeds but disease in others, with damage to gut mucosa and occurrence of diarrhea (126). Together, these recent findings revealed the complex interaction between *Campylobacter* and the chicken host and suggested the need for re-evaluation of the impact of *Campylobacter* on poultry health and welfare.

CONTROL OF *CAMPYLOBACTER* ON POULTRY FARMS

As described above, *Campylobacter* is common in the farm environment and can contaminate poultry houses via many different routes, which makes the prevention of flock colonization a very difficult task. Because the majority of human *Campylobacter* infections are associated with the consumption of chicken meat, control of *Campylobacter* in broilers has received the most attention. In this section, we will summarize preharvest approaches that have been evaluated for the control of *Campylobacter* in broiler production.

Biosecurity and hygiene. Implementing strict biosecurity and good hygiene measures helps to prevent *Campylobacter* from entering the broiler houses from the outside environment. These practices include washing hands before engaging the flocks, designating separate boots and personal gear for different broiler houses, deploying footbaths for disinfection, limiting access to the flocks to only essential personnel, training workers in best hygiene practices, controlling pests such as rodents and insects, thorough decontamination of drinking water delivery systems, maintaining the physical structure of broiler houses, and other practices (114). Wagenaar *et al.* (250) estimated that human incursions into broiler houses can occur on 50 to 150 occasions over the life of a flock. This trafficking, which is prodded by sometimes unavoidable production and maintenance practices, constitutes a significant risk for introducing *Campylobacter* to the flocks. Therefore, adequate biosecurity and hygiene are essential barriers against contamination, and they also serve to limit transmission of the pathogen between different flocks on the same farm and between rotating flocks reared in the same enclosure. Indeed, the decrease of the prevalence of *Campylobacter* from 80% to <40% in broilers was attributed to the implementation of personnel hygiene and broiler house disinfection protocols (91). Furthermore, in a recent study rodent control around broiler houses was associated with lower risk (OR = 0.18, 95% confidence interval [CI] 0.03–0.95) of *Campylobacter* colonization (8). However, even the most-stringent biosecurity measures do not always have a consistent and predictable effect on controlling *Campylobacter*, and their effectiveness in controlling flock prevalence is difficult to assess under commercial settings (15,82,178,194). In addition, stringent biosecurity measures are cost prohibitive, hard to maintain, and their effectiveness varies with production systems (82,207). For example, a study conducted on Finnish poultry farms concluded that biosecurity costs approximately 3.55 Eurocents per bird and claims 8% of the total work time on broiler farms (218). Another example is the use of fly screens, which has been shown to be effective in reducing the introduction of *Campylobacter* into broiler houses (ca. 30% decrease in number of positive flocks) in some northern European countries (99,106). A recent study conducted in Denmark evaluated the long-term effects associated with deploying fly screens in 10 broiler chicken houses (19). After using fly screens, the prevalence of *Campylobacter*-positive flocks dropped from 41.4% to 10.3% (19). Additionally, the typical peak of *Campylobacter* prevalence during summer did not occur (19), further indicating the effectiveness of fly screens in preventing *Campylobacter* from entering into broiler houses. However, the use of fly screens in the United States is not likely to be as effective as in Europe due to the prominent differences in the ventilation systems of poultry houses (e.g., horizontal [tunnel] ventilation in the United States *vs.* vertical ventilation shafts in Europe) (269). Thus, the differences in production practices between countries affect the success of certain biosecurity and hygiene approaches, which poses a significant challenge for evaluating and adopting universal control protocols.

Certain farming practices, such as thinning, may increase the risk of *Campylobacter* contamination and compromise the fidelity of biosecurity approaches (114,250). Thinning is the early removal of a portion of birds to create space for the rest of flock for continued growth (a common practice in the Europe but not in the United States). Therefore, thinning requires the entry of personnel and catching equipment into broiler houses. This increases the risk of *Campylobacter* transmission within and between flocks. It was suggested that thinning was associated with the contamination of 50% of flocks that were previously *Campylobacter*-free (113,250). In a well-designed study, Allen *et al.* (11) reported that 27 flocks became *Campylobacter* positive within 2–6 days of the start of thinning. The authors showed that the farm driveways, transport vehicles, equipment, and personnel were also contaminated with *Campylobacter* before thinning, highlighting the potential risk associated with thinning operations. Furthermore, pulsed-field gel electrophoresis typing indicated a spread of particular strains from one farm to another during thinning via transport vehicles, equipment, and personnel (11).

Treatment of drinking water. Acidification of drinking water was reported to decrease the risk of *Campylobacter* colonization in broiler flocks (8). Recently, a large-scale study was conducted to evaluate commercially available organic acids as water additives. The authors concluded that drinking water treated with organic acids can lower the load of *Campylobacter* (without negatively affecting the production parameters or animal welfare) in broiler ceca with a mean reduction of 4.25 $\log_{10}$ CFU compared with the control group at slaughter age, although no reduction was observed on postchilled carcasses (133). It was also reported that the addition of organic acids, specifically lactic acid, to drinking water during feed withdrawal significantly reduced the isolation incidence of *Campylobacter* (62.3% in treatment *vs.* 85.1% in the control groups) recovered from crop samples (38). In another study, water acidification using a commercially available product that contained formic acid, acetic acid, lactic acid, and propionic acid among other ingredients significantly decreased *Campylobacter* transmission between infected and susceptible broilers (with the transmission parameter being 0.075 for control and 0.011 for treatment per day) which were spatially separated (242). However, when transmission was simulated by eliminating spatial separation between infected and susceptible birds, water acidification did not have an impact (242). In another study, most of the experimentally infected young broilers remained colonized with *Campylobacter* after the addition of organic acid to the drinking water (47).

The observations above suggest that the addition of organic acids to drinking water has a partial effect in terms of controlling *Campylobacter* colonization and transmission, suggesting that water acidification may be combined with other approaches to optimize the impact on this organism. It should be noted that other water treatments, such as chlorination or the addition of monocaprin, were comparable to organic acids in reducing *Campylobacter* counts in cloacal samples but did not affect transmission between broilers and the overall prevalence (120,233). It is important to note that *Campylobacter* in water can be associated with other organisms such as protozoa, which are more resistant to chlorine residues in comparison to bacteria. For example, protozoa-ingested *Campylobacter* was >50-fold more resistant to free chlorine (144).

Litter treatment. The acidification of litter has also been evaluated to control *Campylobacter* in broilers in the United States. For example, Line (157) treated *Campylobacter*-contaminated litter with two commercially available chemicals, aluminum sulfate (Alum) and sodium bisulfate, which reduced the pH of the litter.

The treated litter was then used to rear noninoculated birds. The treatments were successful in decreasing *Campylobacter* colonization frequency (from 90% in the controls to 10% in the treatment groups) and cecal loads (up to 5 $\log_{10}$ reduction) as well as carcass contamination (from 38% to 0%). Subsequently, Line and Bailey (158) also tested the treatments on commercial broiler farms and reported that both treatments only caused a slight delay in *Campylobacter* colonization of broiler chicks and were not successful in significantly reducing *Campylobacter* in unprocessed, whole-carcass, rinse samples analyzed at the end of production. The major complication associated with the aforementioned treatments is that the litter pH was only reduced for a limited time, after which the effect on the pH was lost (157,158). Therefore, treatments that can maintain low pH in litter throughout the broilers' rearing period might prove to be more effective for the control of *Campylobacter* in commercial operations.

Feed additives. Similar to their use in water, organic acids have been also used for the acidification of chicken feed. This is based on the premise that ingested organic acids might lower the pH in the chicken gut, rendering this niche more hostile to *Campylobacter* colonization. This is plausible because under laboratory conditions *C. jejuni* can tolerate pH levels below 2.5 or 3 for only a short time (less than 30 and 60 min, respectively) (30,200). The pHs of the chicken gizzard, ceca, and intestines are 3–3.5, 6–7, and 6–8.5, respectively (201); therefore, for instance, if acidified feed can further reduce the pH of the gizzard, orally ingested *Campylobacter* might not be able to survive in the gizzard and establish colonization in the intestine. In general, *in vivo* application of acidified feed had limited success in effectively reducing *Campylobacter* colonization of broilers (114). However, in one study it was reported that a combination of 2% formic acid and 0.1% potassium sorbate administered in feed totally prevented colonization of broilers by *C. jejuni* (220). The same study found a substantial effect (i.e., 16%–25% reduction) of the treatment on a bird's body weight. However, this approach has not been tested yet using a more-diverse set of *C. jejuni* isolates or under field conditions on commercial farms. It is also interesting to note that the association of *Campylobacter* with amoebae increases its tolerance to acids (17). Specifically, *C. jejuni* coincubated with *Acanthamoeba polyphaga* were able to survive at pH 2 for 5 hr (17).

Application of bacteriophages. The potential use of bacteriophages for control of *Campylobacter* in poultry has been examined in multiple studies. In one study, a 2-log decline in the counts of *Campylobacter* in cecum of infected chickens was observed 48 hr after bacteriophage application (74). Wagenaar *et al.* (251) evaluated treatment of *Campylobacter*-infected chickens with bacteriophages and observed an immediate reduction (approximately 3 logs) in the number of *Campylobacter* in ceca after oral administration of bacteriophages. However, the impact of bacteriophages on *Campylobacter* load declined after a few days and eventually stabilized at a level that was only 1 log lower than the CFU in the control birds that were untreated with bacteriophages (251). The limited success with phages was corroborated by other studies that showed no significant decline in *Campylobacter* colonization of bacteriophage-treated broilers at later time points (35 and 42 days post application) (81). Furthermore, great variations in efficacy were seen with different combinations of bacteriophages and *Campylobacter* strains in in-vivo trials (159).

These studies indicate that bacteriophages are at least partly effective for reducing *Campylobacter* in broilers; however, the efficiency was inconsistent and temporally constrained, which could be explained by multiple factors. For example, *Campylobacter* may develop resistance to bacteriophages during treatment and, consequently, resistant strains establish in the chicken host, negating the initial bacteriophage-mediated reduction in colonization (132). Secondly, bacteriophages may be strain-specific and only effective against certain *Campylobacter* strains (159). This is a particularly challenging problem considering the diversity of *Campylobacter* strains in broilers, the sheer magnitude of on-farm production (size of flocks), and the short growth cycle of commercial broilers. So far there have been only a limited number of on-farm studies and *in vivo* trials that span the growth cycle of broilers, which indicated that phage treatment in general had a limited effect on *Campylobacter* control. Additionally, it was reported that bacteriophages that were effective against *Campylobacter in vitro* did not impact colonization in broilers (132,159), yielding a discrepancy between *in vitro* and *in vivo* observations. Furthermore, the bulk production of phages using *Campylobacter* is of low efficiency, which further complicates commercial application (132). Therefore, the application of bacteriophages to control *Campylobacter* in live broilers needs further improvements. Despite these hurdles, it is predicted that bacteriophages may be useful, perhaps as a complementary tool, to reduce *Campylobacter* in the food chain. For example, it has been suggested that bacteriophages may be applied right before chickens are due for slaughter or directly on carcasses, which might reduce the emergence of phage-resistant *Campylobacter* strains and the *in vivo* variability of their effects (132).

Immune intervention. It has been well established that infection with *C. jejuni* in poultry can induce protective immunity against reinfection by *Campylobacter*, supporting the feasibility of developing immune interventions against *Campylobacter* colonization in poultry. However, to date there are still no effective and consistent immune interventions, primarily due to the lack of understanding of the protective immunity, the great antigenic variability of different *Campylobacter* strains, and the inability of current vaccination regimens to induce a strong and persistent mucosal immune response in chickens.

Identification of immunogenic and protective antigens in *C. jejuni* is a critical step for the development of effective intervention measures. Various candidates, most of which are outer membrane proteins required for *Campylobacter* pathobiology, have been identified and summarized in a previous review (156). Recently, Yeh *et al.* (264) examined reactivity of broiler chicken sera to 15 selected recombinant chemotactic proteins and showed that the chemotactic protein Cj0473 is a potential candidate for immune intervention against *Campylobacter* in broilers. Using *in vivo*-induced antigen technology, Hu *et al.* (122) recently identified the genes expressed *in vivo* during *C. jejuni* infection of the chicken host and suggested that these genes may be potential vaccine candidates for immunization against *Campylobacter* in poultry.

Two types of immune interventions have been pursued to reduce *Campylobacter* load in poultry: passive immunization and active vaccination of broilers. Regarding the passive immunization, several recent studies (7,115,186) evaluated oral administration of *Campylobacter*-specific chicken egg-yolk-derived antibodies for reduction of *C. jejuni* colonization. The studies showed ineffectiveness (186) or partial success (ca. 5 $\log_{10}$ CFU reduction in ceca) (115) of this approach. Riazi *et al.* (191) produced a unique, pentavalent, single-domain antibody directed against *C. jejuni* flagella and observed that oral administration of the antibodies reduced *C. jejuni* colonization in the ceca (ca. 3 $\log_{10}$ CFU reduction) without impacting the chicken body weight gain.

Most of the previous studies on immunization focused on active vaccination, which has been comprehensively reviewed in recent

articles (66,88,114,156). Identification of immunogenic and potentially protective antigens in *C. jejuni* has resulted in recent vaccine development being focused on subunit vaccines using various delivery systems such as oral live *Salmonella*-vectored vaccine (62,63,149,150,156,239), *Eimeria* parasite vector-based live vaccine (53), and nanoparticle-encapsulated vaccine administered via oral route (13) or intranasal route (123). Despite extensive efforts, chicken trials showed limited success of different vaccination regimens. Clearly, the short life span of broiler chickens (~6–7 wk) and the need to induce a protective immunity in the intestinal tract have posed a significant challenge for development of vaccines against *Campylobacter* in chickens (54,88,253). In addition two factors, the cost and simplicity of administration, should be considered for *Campylobacter* vaccines used in poultry. The *in ovo* vaccination approach may be explored for *Campylobacter* vaccine development because vaccination at embryonation day 18 has proven to be a safe, effective, and convenient method for protecting chickens against viral, bacterial, and protozoal diseases in poultry (193).

Bacteriocins. Bacteriocins are a group of antimicrobial peptides (AMPs) produced by bacteria with narrow or broad host ranges (56,110). Bacteriocins have considerable potential for the design and production of a new generation of antimicrobials against various pathogens (156). In particular, significant progress has been made for the discovery of potent anti-*Campylobacter* bacteriocins from commensal bacteria isolated from the chicken intestinal tract (156). Although bacteriocins dramatically reduced *C. jejuni* colonization in poultry (e.g., up to total elimination of detectable levels of colonization), practical application of this approach for on-farm control of *Campylobacter* has not been evaluated, likely due to the production cost of bacteriocins (156).

AMPs produced by the chicken host, such as defensins and cathelicidins, also have potent antimicrobial activity against diverse pathogens including *Campylobacter* (121). However, using purified chicken AMPs for pathogen control is not a cost-effective option. Recently, dietary modulation of the synthesis of endogenous chicken AMPs has emerged as a novel antibiotic-alternative approach to antimicrobial therapy (267). Notably, a group of short-chain fatty acids (e.g., butyrate) displayed a strong capacity to augment the expression of nearly all 14 chicken endogenous AMPs, and oral administration of butyrate significantly reduced colonization of *Salmonella* Enteritidis (nearly a 10-fold reduction in the bacterial count) in the chicken cecum (235). More desirably, butyrate could act synergistically with several other classes of dietary compounds in inducing AMP expression in chickens (236). Together, these recent findings suggest the potential of dietary compounds in boosting poultry immunity and clearance of food-borne pathogens including *Campylobacter*. Thus, innate immunity-boosting strategies using dietary compounds should be further explored for the control of *Campylobacter* in poultry.

Competitive exclusion. Competitive exclusion is the introduction of agents, including defined or undefined microflora, to enhance the resistance of broilers to *Campylobacter* colonization (114,250,252). In general, the use of probiotics in competitive exclusion trials has had inconsistent results (90,103,179,198). For example, the competitive exclusion product Broilact® (Nimrod Veterinary Products Ltd., Upper Rissington, U.K.; which is a ''preparation of freeze-dried bacteria collected from the intestine of a normal adult fowl''), when used alone or in combination with other facultative anaerobic bacteria was found to have variable effects in prevention and reduction of *Campylobacter* colonization in the ceca of broiler chickens in laboratory experiments (6,103). In another example, it was reported that the administration of *Bifidobacterium longum* PCB 133 in feed did reduce *C. jejuni* by approximately 1 log in the feces of experimentally infected chickens (210). In a follow-up study, *B. longum* PCB 133 was combined with a prebiotic (galactooligosaccharide, which was shown to promote *Bifidobacterium* spp. but reduced *Campylobacter* in broilers by itself), but no noticeable increase in effectiveness against *Campylobacter* colonization was observed (18). In a recent study, the multispecies probiotic product PoultryStar® (Biomin, Herzogenburg, Austria), which contained *Enterococcus faecium*, *Pediococcus acidilactici*, *Bifidobacterium animalis*, *Lactobacillus salivarius*, and *Lactobacillus reuteri*, significantly reduced *Campylobacter* loads in the ceca of broilers (up to more than 5 $\log_{10}$ CFU) at 8 and 15 days postchallenge (90). For practical application, competitive exclusion must surpass the complexity and diversity of the *Campylobacter* populations circulating in the broiler host, and the competing agent(s) must be viable in the chicken gut environment long enough to sustain the effect until the slaughter age of broilers.

Genetic resistance. Genetic resistance is the intrinsic property of the chicken host to resist colonization by *Campylobacter*. Several studies reported variable susceptibilities of different chicken lines to colonization by *Campylobacter* (33,154,155,229). Notably, it was recently reported that the resistance of chickens to *Campylobacter* was associated with the inhibition of a small, GTPase-mediated signal transduction as well as the tumor necrosis factor receptor superfamily genes (154). This finding might allow for the selective breeding of *Campylobacter*-resistant broilers in the future. Additionally, a recent study showed that breeds of broilers affected disease manifestation, with *Campylobacter* as a commensal in some breeds but as a pathogen in other breeds (126). Selective breeding may produce chickens that are resistant to *Campylobacter*, but it should not harm production traits and should not increase the susceptibility to ailments or other pathogens.

CARCASS CONTAMINATION AND POSTHARVEST INTERVENTIONS

The high numbers of *Campylobacter* in the intestinal tract results in contamination of poultry carcasses during the slaughter process due mainly to spillage of fecal material at defeathering and evisceration as well as to cross-contamination from the abattoir environment (9,27,49,75,95,124,136,199). The prevalence of *Campylobacter* on poultry carcasses at the end of the processing line (postchill) is usually over 50%, varying from 0% to 100% worldwide (26,49,69,70,100,125,160,165,192,231,256,266). In the United States, several studies reported that a large percentage of processed broiler carcasses were contaminated with high numbers of *Campylobacter* (26,39,177,213,231). Carcass contamination by *Campylobacter* is attributable to the farm of origin, as a high prevalence on-farm is usually associated with high-level carcass contamination in processing plants (9,27,124,136,199). The reported levels of *Campylobacter* contamination of carcasses vary with countries, seasons, and studies (26,49,69,70,100,231).

Poultry in processing plants are subjected to multiple processing steps including stunning and bleeding, scalding, defeathering, evisceration, washing, chilling, and postchill treatments, all of which affect carcass contamination by *Campylobacter*. Processing practices and control measures taken at abattoirs can significantly reduce cross-contamination and overall carcass contamination by *Campylobacter* in the final meat products. The FSIS-USDA released the third edition (2010) of a compliance guideline comprehensively describing the recommendations and best management practices for the control of *Campylobacter* and *Salmonella* at preharvest and

postharvest levels (85). Although the guideline clearly indicates the importance of preharvest production practices for food safety, it also recognizes the shortcomings related to on-farm–based interventions and strongly encourages the adoption of best management practices during slaughter operations for effective control of *Campylobacter* contamination of poultry meat (85).

Numerous studies (both laboratory and commercial plant-based) investigated potential interventions to reduce *Campylobacter* counts on poultry carcasses (9,26,28,57,100,199,250). The evaluated measures include freezing, hot water treatment, irradiation, and chemical decontamination. Depending on the specific processing stage, the use of several practices, such as treatment time, temperature, pH, direction of water flow, and antimicrobial solution, can greatly affect the level of carcass contamination by *Campylobacter* (9,28,57). In general, prevalence and level of carcass contamination by *Campylobacter* in the processing plant increase after defeathering and evisceration but decrease after scalding and chilling (26,69,100,199,200). High pH (9.8) scald appears more effective than does standard pH (6.8) scald in reducing the level of *Campylobacter* on broiler carcasses (26,28). Because fecal release occurs readily during defeathering and evisceration, general equipment sanitation and multiple rinsing of equipment and carcasses during and after each step with chemicals (such as 20 ppm chlorine, sodium bisulphate, cetylpyridinium chloride, lactic acid, and trisodium phosphate) have been shown to be effective in reducing carcass contamination (85). A prechill rinse with clean water is important to prevent carryover of these chemicals into the chiller. Carcasses must be free of fecal contamination before placement in the chiller, as mandated by the FSIS. During the immersion chilling process the use of antimicrobials is highly encouraged; the pH of the chlorine wash (available free chorine should be 20–50 ppm) should be maintained between 6.0–6.5 at a temperature of less than 40 F (85). During this step, a combination of other chemicals (such as chlorine dioxide), removal of organic matter in water, and using clean water also reduce pathogen load. Air chilling was found to be more effective than water chilling for reducing *Campylobacter* in some studies, but this was not observed in others (70,101). Postchill antimicrobial rinses with potable water and dips in antimicrobial solutions can be used to further reduce the level of *Campylobacter* contamination in poultry meat.

The following FDA-approved chemicals can be used for processing poultry meat without additional approval from the FSIS (85): acidified sodium chloride (ASC); calcium hypochlorite, cetylpyridinium chloride; chlorine gas; chlorine dioxide; 1,3-dibromo-5,5-dimethylhydantion (DBDMH); a solution of citric and hydrochloric acids; a blend of citric, phosphoric, and hydrochloric acids; a lactic acid bacteria mixture consisting of *Lactobacillus acidophilus*, *Lactobacillus lactic*, and *Pediococcus acidilactici*; ozone; sodium hypochlorite; and trisodium phosphate (TSP). It should be noted that although chemical decontamination of poultry carcasses at the processing plant is commonly practiced in the United States, it is not allowed in EU countries (70,85,249).

As mentioned above, both the prevalence and quantity of *Campylobacter* on poultry carcasses at the end of processing line (postchill) in slaughterhouses can vary markedly. The variation is influenced by plant-specific factors (26,69,70,100,160,199), suggesting interventions can be applied in processing plants to reduce carcass contamination by *Campylobacter* at each step as well as on the final product. Well-designed prospective studies that map the impact of each processing step (slaughter, scald, defeather, eviscerate, wash, chill, etc.) on contamination will allow the identification of critical control points, which will be valuable for the design and implementation of targeted interventions to reduce *Campylobacter* contamination of carcasses.

ANTIMICROBIAL RESISTANCE IN *CAMPYLOBACTER* FROM POULTRY

There have been many reports on the prevalence of antibiotic-resistant *Campylobacter* from poultry. For detailed information, please refer to the review papers (89,92,102,128,161,250,268). As a commensal of birds, *Campylobacter* colonization in poultry does not require antibiotic treatment; however, *Campylobacter* is highly prevalent in poultry, and antibiotics administered for prevention and control of poultry diseases can select antibiotic-resistant *Campylobacter* which can be transmitted to humans via contaminated poultry meat. For treating human Campylobacteriosis, fluoroquinolones and macrolides are the drugs of choice (12). Thus, *Campylobacter* resistance to these two classes of antibiotics is a major concern for public health.

In the mid-1990s, the FDA licensed two fluoroquinolones (sarafloxacin and enrofloxacin) for treatment of respiratory diseases in poultry. Several years later, investigations revealed a rapid increase of sarafloxacin and enrofloxacin resistance in *Campylobacter* from poultry that were also resistant to ciprofloxacin and other fluoroquinolones used in human medicine (76,101,180). As a result of these observations, at least in part, use of fluoroquinolones in poultry production is now prohibited in the United States (180). Resistance to fluoroquinolones in *Campylobacter* from poultry is considerably high in some reports, and varies widely from country to country, with up to 98% resistance rates in some regions (48,102). In countries such as Spain and Thailand, high rates of fluoroquinolone resistance (80%–99%) in *Campylobacter* isolates from broiler ceca were reported (49,204), whereas much-lower resistance rates (0%–11%) were observed in *Campylobacter* isolates from broiler flocks in countries such as Australia, Denmark, and Norway (128,173,184). Both *C. jejuni* and *C. coli* isolates from conventional turkey flocks were shown to carry a high level of ciprofloxacin resistance (51% and 97.1%, respectively) in studies conducted in the eastern United States (98,152). In the United States, as reported by the National Antimicrobial Resistance Monitoring System (NARMS), resistance rates to ciprofloxacin among *C. jejuni* isolates from chicken carcasses at slaughter have been around 20% between 2001–2010, with an overall upward trend from 20.3% in 2001 to 23.1% in 2010 (80). Similar trends in the resistance rates have also been observed in the NARMS report for *C. jejuni* from retail chicken, although ground turkey at retail were reported to have an overall higher resistance rate to fluoroquinolones (~50%). In general, *Campylobacter* from conventional poultry productions have higher rates of antimicrobial resistance as compared with those from organic productions (208). For example, a study conducted in the United States (162) found that conventional poultry (especially turkey) farms had a significantly higher prevalence of antibiotic-resistant *Campylobacter* than did organic poultry farms, and the difference was especially greater with fluoroquinolone resistance (~50% *vs.* 2%, respectively). It was also reported that for retail poultry meat, the proportion of fluoroquinolone-resistant *Campylobacter* isolates was significantly less from organic chickens than from conventional broilers (5% *vs.* 20%) (61). However, a recent study from Portugal on the antimicrobial resistance of *Campylobacter* isolates from different chicken production systems (including organic, extensive indoor, and intensive productions) at slaughter indicated an overall high rate (>77%) of fluoroquinolone resistance (83).

Macrolide antibiotics are occasionally used in water for therapeutic purposes (e.g., for treatment of mycoplasma infections and necrotic enteric) in poultry (77,169). In *Campylobacter*, modification of the ribosomal target leading to macrolide resistance occurs mainly by point mutations in the 23S rRNA or in ribosomal proteins L4 and L22 (or both) (92,161). However, a ribosomal RNA methylase enzyme (ErmB) that confers macrolide resistance has also been identified recently in *Campylobacter* isolates (~4%) from various animal species including chickens and ducks in China (189,253). In general, the resistance rate to macrolides among *Campylobacter* isolates in poultry, especially in *C. jejuni*, is considerably lower than that for fluoroquinolones. However, macrolide resistance has also been increasingly reported, especially among *C. coli* isolates, with resistance rates as high as 96% in some studies (102,128,162,165). In two studies conducted in eastern United States, *C. jejuni* from conventionally grown turkey flocks did not show any erythromycin resistance (98), but a very high rate (95.6%) of resistance to the same drug was detected in *C. coli* from conventional turkeys (151). Similarly, 94% of *C. coli* from broiler chickens was found to be resistant to erythromycin (165). In contrast, a recent study from Portugal (83) reported that chicken *C. jejuni* isolates had a significantly higher rate of erythromycin resistance than did *C. coli* (35.4% *vs.* 13.3%). High levels of erythromycin resistance (48% and 88%, respectively) were also observed in *Campylobacter* isolates from commercially raised chickens (industrial and free range, respectively) in South Africa in 2012, although *Campylobacter* isolates from the chickens in rural production systems tested in the same study did not manifest any resistance to this drug (29). The NARMS report (80) indicates an overall very low-level erythromycin-resistance rate (it fluctuated between 0%–10% from 2001 to 2010) in *C. jejuni* isolates recovered from chicken carcasses at slaughter and from retail poultry meat in the United States. With respect to macrolide resistance rates in *Campylobacter* from conventional *vs.* organic poultry operations, there appears to be no clear distinction. In a comprehensive study from the United States, none of the isolates from conventional chicken farms were found to be resistant to erythromycin, although 9% of isolates from organic broilers were resistant to this drug (162). On the contrary, the same study showed that organic turkey farms had significantly less erythromycin-resistant *Campylobacter* than did conventional turkey farms (~5% and 80% resistance rates, respectively), suggesting macrolide resistance in *Campylobacter* varied substantially between production types (broiler *vs.* turkey). Also interestingly, organic chicken carcasses from retail stores surveyed in Maryland were found to harbor a substantially higher percentage of erythromycin-resistant *Campylobacter* than did conventional chickens (49% *vs.* 36% resistance rate) (61). Additionally, a survey of *Campylobacter* from prepackaged chickens at London supermarkets found overall high levels of resistance (>80%) to erythromycin in both organic and conventional products (224). Together, these studies clearly indicate a rising trend of macrolide-resistant *Campylobacter*, underlying the need for heightened efforts to develop effective interventions. Different from fluoroquinolone resistance, macrolide-resistant *Campylobacter* shows a substantial fitness cost in the chicken host in the absence of antibiotic selection (163,164), which suggests the possibility of controlling macrolide-resistant *Campylobacter* via prudent use of antibiotics.

CONCLUSIONS AND FUTURE DIRECTIONS

Significant advancement has been made during the past years in understanding the epidemiology and ecology of *Campylobacter* in poultry as well as in evaluating intervention strategies. As a commensal of birds, *Campylobacter* is well adapted in the poultry intestinal tract. This commensal interaction elicits only a moderate immune response of tolerogenic nature in the avian gut, resulting in persistent colonization with high numbers of the organism. Due to the fact that *Campylobacter* is commonly present in the farm environment and can be introduced into poultry houses in many ways, it is extremely difficult to keep chicken flocks free of *Campylobacter* during the preharvest production stage. Postharvest intervention in the slaughtering stage is also challenging due to the high numbers of *Campylobacter* in feces and the unavoidable fecal contamination of carcasses during the slaughtering process. Each of the control strategies discussed above has certain potentials, but none may be sufficient when applied individually. Therefore, it might be more effective when multiple measures are used in combination. However, use of multiple strategies may prove to be difficult due to practical and economic reasons. Thus, additional efforts are critically needed to develop practical and effective interventions. To accomplish this difficult task, future research may be targeted to several promising areas. For example, it has been observed that young flocks are always free of *Campylobacter* and that some chicken farms are consistently negative with this organism. If the reasons for the lack of infection are elucidated, they may be exploited to control *Campylobacter* on farms. Also, understanding the interaction of *Campylobacter* with the poultry immune systems may provide clues for eliciting protective immunity and optimizing immunization strategies. Additionally, some measures such as bacteriocins and bacteriophages may be evaluated for application right before the slaughter to significantly reduce the pathogen load in the intestinal tract. Finally, systematic analysis of the critical control points in slaughterhouses may identify effective measures to control carcass contamination. These enhanced research and development efforts may eventually ripen into a ''magic'' intervention strategy that allows effective control of *Campylobacter* in poultry, thus improving the safety of food products.

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