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Global Epidemiology of *Campylobacter* Infection

Nadeem O. Kaakoush,[a] Natalia Castaño-Rodríguez,[a] Hazel M. Mitchell,[a] Si Ming Man[a,b]

School of Biotechnology and Biomolecular Sciences, The University of New South Wales, Sydney, NSW, Australia[a]; Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA[b]

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Address correspondence to Si Ming Man, SiMing.Man@StJude.org.

N.O.K. and N.C.-R. contributed equally to this article.

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SUMMARY

Campylobacter jejuni infection is one of the most widespread infectious diseases of the last century. The incidence and prevalence of campylobacteriosis have increased in both developed and developing countries over the last 10 years. The dramatic increase in North America, Europe, and Australia is alarming, and data from parts of Africa, Asia, and the Middle East indicate that campylobacteriosis is endemic in these areas, especially in children. In addition to *C. jejuni*, there is increasing recognition of the clinical importance of emerging *Campylobacter* species, including *Campylobacter concisus* and *Campylobacter ureolyticus*. Poultry is a major reservoir and source of transmission of campylobacteriosis to humans. Other risk factors include consumption of animal products and water, contact with animals, and international travel. Strategic implementation of multifaceted biocontrol measures to reduce the transmission of this group of pathogens is paramount for public health. Overall, campylobacteriosis is still one of the most important infectious diseases that is likely to challenge global health in the years to come. This review provides a comprehensive overview of the global epidemiology, transmission, and clinical relevance of *Campylobacter* infection.

INTRODUCTION

Campylobacter species are Gram-negative spiral, rod-shaped, or curved bacteria with a single polar flagellum, bipolar flagella, or no flagellum, depending on the species (1). *Campylobacter* species are non-spore-forming, are approximately 0.2 to 0.8 by 0.5 to 5 μm, and are chemoorganotrophs which obtain their energy sources from amino acids or tricarboxylic acid cycle intermediates (2). Most *Campylobacter* species grow under microaerobic conditions and have a respiratory type of metabolism; however, several species (*Campylobacter concisus*, *Campylobacter curvus*, *Campylobacter rectus*, *Campylobacter mucosalis*, *Campylobacter showae*, *Campylobacter gracilis*, and, to a certain extent, *Campylobacter hyointestinalis*) require hydrogen or formate as an electron donor for microaerobic growth. In addition, certain species prefer anaerobic conditions for growth.

The *Campylobacter* genus was established in 1963 following the renaming of *Vibrio fetus* to *Campylobacter fetus*, forming the type species of this genus (3). The *Campylobacter* genus belongs to the family *Campylobacteraceae*, the order *Campylobacterales*, the class *Epsilonproteobacteria*, and the phylum *Proteobacteria*. Since its first description, the genus has grown to include several important human and animal pathogens that are primarily classified through phylogenetic means. The genus *Campylobacter* consists of 26 species, 2 provisional species, and 9 subspecies (as of December 2014).

Campylobacter jejuni is a major cause of gastroenteritis worldwide. Moreover, *C. jejuni* infection may lead to autoimmune conditions known as Guillain-Barré syndrome (GBS) and Miller Fisher syndrome. Many *Campylobacter* species are known pathogens in humans and animals (1). In humans, *Campylobacter* species have been associated with a range of gastrointestinal conditions, including inflammatory bowel diseases (IBD), Barrett's esophagus, and colorectal cancer (Fig. 1) (1). They have also been reported to be involved in extragastrointestinal manifestations, including bacteremia, lung infections, brain abscesses, meningitis, and reactive arthritis, in individual cases and small cohorts of patients (1). A full list of the clinical manifestations associated with *Campylobacter* infection is presented in Table 1. The precise role of *Campylobacter* species in the development of these clinical conditions is largely unknown. In this review, we describe the latest global epidemiological landscape of *C. jejuni* and other *Campylobacter* species in gastroenteritis and other diseases. We also discuss the modes of transmission and biocontrol methodologies to prevent transmission of campylobacteriosis.

GASTROENTERITIS

C. jejuni and *C. coli* are established causes of diarrhea in humans. A human experimental infection study revealed that the rate of colonization increased with increasing doses of *C. jejuni*, whereas the development of illness did not (4). Infection with a dose as low as 800 CFU resulted in diarrhea in some volunteers (4). However, it has been speculated further that the dose of *C. jejuni* required for the development of campylobacteriosis can be as low as 360 CFU (5). Mathematical modeling suggested that an intermediate dose of 9×10^4 CFU/ml has the highest ratio of illness to infection (6). In contrast, an association between dose and occurrence of disease was observed in humans experimentally infected with *C. jejuni* strain 81-176. In addition, exposure to *C. jejuni* strain 81-176 offered only short-term protection (7). This can be reconciled by the fact that the severity of disease, dose-response relationship, and illness/infection ratio are dependent, at least in part, on the strain used. These strain-specific differences were clearly observed when experimental infection of naive individuals with *C. jejuni* strain CG8421 failed to offer protection against a second bout of campylobacteriosis upon rechallenge with the same strain (8). Interestingly, an immunocompetent adult experimentally infected with *C. jejuni* experienced recrudescence of the infection at the conclusion of antibiotic therapy (9), suggesting that the incidence of recurrent infection may be underestimated.

Patients with *C. jejuni* or *C. coli* infection experience acute watery or bloody diarrhea, fever, weight loss, and cramps that last, on average, 6 days (1). Gastroenteritis induced by *C. coli* is clini-

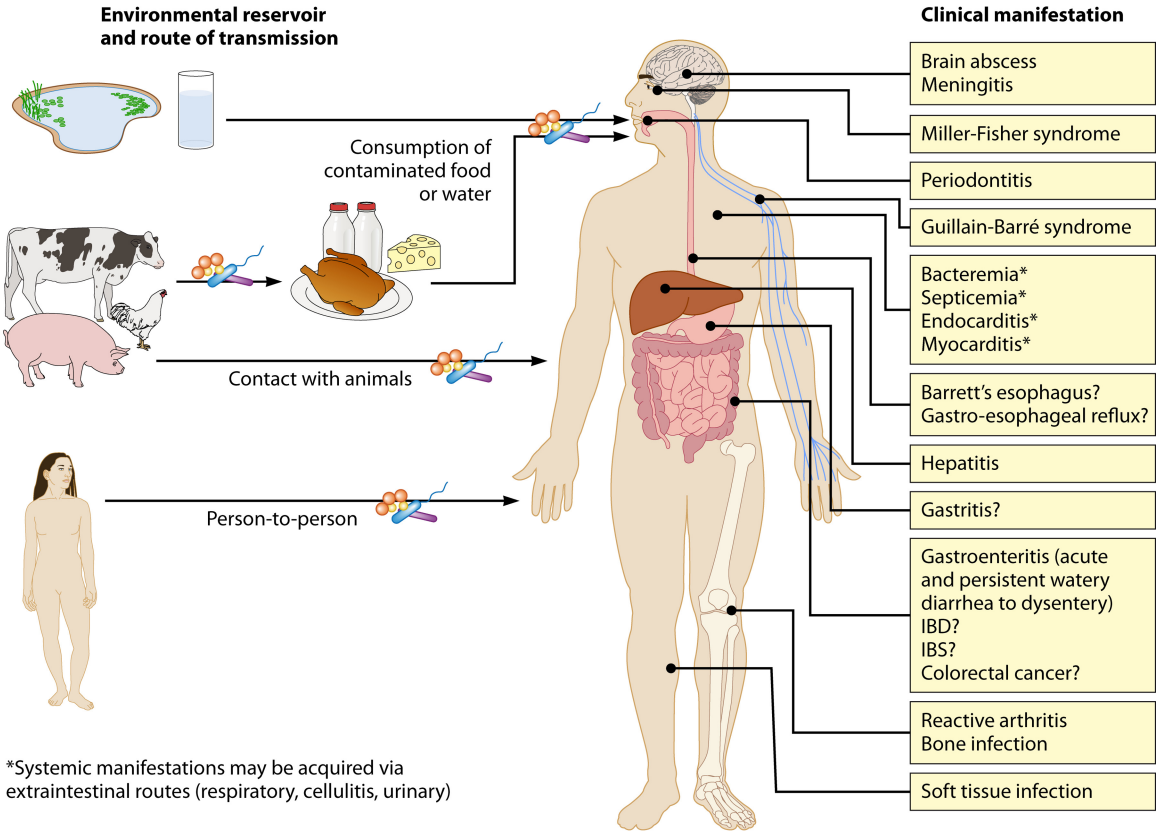

FIG 1 Environmental reservoirs, routes of transmission, and clinical manifestations associated with *Campylobacter* species. *Campylobacter* species can be transmitted to humans through consumption of undercooked or contaminated food or via contact with animals. Tap, bore, and pond waters are also sources of *Campylobacter* species. Person-to-person transmission (fecal-oral or via fomites) can occur. Ingestion of a sufficient dose of organisms via the oral-gastric route may lead to one or more gastrointestinal and/or extragastrointestinal manifestations; the outcome is dependent on the species or strains of *Campylobacter* involved in the infection. Abbreviations: IBD, inflammatory bowel diseases; IBS, irritable bowel syndrome. Question marks indicate conditions for which a role for *Campylobacter* is implicated but not certain.

cally indistinguishable from that by *C. jejuni*. The onset of symptoms usually occurs 24 to 72 h following ingestion and may take longer to develop in those infected with a low dose. The peak of illness can last 24 to 48 h and may include abdominal pain that mimics appendicitis (10). Polymorphonuclear leukocytes and blood (gross or microscopic) can be observed in the stool, and diffuse inflammatory colitis is present in colonic biopsy specimens from infected patients (10). While infection with *C. jejuni* or *C. coli* can occur in patients of all ages, a recent study from Denmark showed that infection is more prevalent in toddlers (1 to 4 years) and young adults (15 to 24 years) than in other age groups (11). A recent comparison of the characteristics of patients infected with *C. jejuni* or *C. coli* indicated that slightly older patients (34.6 years versus 27.5 years) and those who traveled abroad were at a greater risk of being infected with *C. coli* than with *C. jejuni* (12). Studies have also shown that infections with *C. jejuni* and *C. coli* are more common during the summer months (11, 13). Although *C. coli* is less prevalent than *C. jejuni* in many geographic regions, *C. coli* infections can contribute as many as 25% of all gastroenteritis cases caused by *Campylobacter* species (14–18).

C. concisus, *Campylobacter ureolyticus*, *Campylobacter upsaliensis*, and *Campylobacter lari* are known as "emerging *Campylobacter* species," a term used to describe their underappreciated roles in human and animal diseases. Emerging *Campylobacter* species are likely to contribute to the etiology of gastroenteritis, especially in cases which have no known association with other established pathogens (1, 19–21). Furthermore, many diagnostic laboratories fail to detect emerging *Campylobacter* species owing to a lack of the specialized cultivation techniques required to culture these organisms, including the use of microaerobic or anaerobic conditions enriched with hydrogen (1). Indeed, introduction of hydrogen as part of routine microaerobic culture for stool samples at a University Hospital in Bern, Germany, resulted in a significant increase in the rate of isolation of *C. concisus* (22). As a consequence, the incidence of *C. concisus* detection rose from 0.03 to 1.92%.

Patients infected with *C. concisus* and certain *Campylobacter* species other than *C. jejuni* and *C. coli* generally experience milder symptoms, with fewer individuals reporting fever, chills, weight loss, and mucus and blood in their stools than those infected with *C. jejuni* and *C. coli* (1, 23). In general, the milder severity of symptoms has been found to correlate with the low levels of fecal calprotectin in those infected with *C. concisus* (median, 53 mg/kg of feces; interquartile range, 20 to 169 mg/kg). For comparison, fecal calprotectin levels are higher (median, 631 mg/kg; interquartile range, 221 to 1,274 mg/kg) in those infected with *C. jejuni* or *C. coli* (24). Symptoms associated with *C. concisus* infection tend to be more persistent than those of *C. jejuni* or *C. coli* infection, with

TABLE 1 Species within the genus *Campylobacter* and their clinical relevance to humans (as of December 2014)[c]

Campylobacter species[a]	Clinical manifestations
C. coli	Established pathogen in gastroenteritis; also found in blood, meningitis, and acute cholecystitis
C. concisus	Emerging pathogen associated with gastroenteritis and IBD (Crohn's disease and ulcerative colitis); also found in Barrett's esophagitis, blood, and brain abscess
C. curvus	Found in gastroenteritis, ulcerative colitis, Barrett's esophagitis, blood, liver, and bronchial abscesses
C. fetus[b]	Associated with bacteremia; also found in gastroenteritis, brain abscesses, epidural abscess aspirate, cerebrospinal fluid, cellulitis, endocarditis, mycotic aneurysm of the abdominal aorta, and peritonitis
C. gracilis	Potential periodontal pathogen; also found in IBD, head and neck infection, and brain abscess
C. hominis	Found in blood and IBD (possibly a commensal in the intestine)
C. helveticus	Found in gastroenteritis
C. hyointestinalis	Found in gastroenteritis and blood
C. insulaenigrae	Found in gastroenteritis and blood
C. jejuni	Established pathogen in gastroenteritis and possible predisposing agent in IBD, postinfectious IBS, and celiac disease; infection may result in sequelae in the forms of Guillain-Barré syndrome, Miller Fisher syndrome, Bell's palsy (unilateral facial paralysis), and reactive arthritis; found in IBD, blood, myocarditis, meningitis, acute cholecystitis, urinary tract infection, and acute febrile illnesses associated with leukopenia or thrombocytopenia
C. lari	Associated with gastroenteritis; also found in blood
C. mucosalis	Found in gastroenteritis
C. rectus	Putative periodontal pathogen; also found in gastroenteritis, IBD, vertebral abscess, blood, necrotizing soft tissue infection, and pus
C. showae	Found in IBD, intraorbital abscess, and blood
C. sputorum	Found in gastroenteritis, axillary abscess, and blood
C. upsaliensis	Emerging pathogen in gastroenteritis; also found in breast abscess, blood, and placenta
C. ureolyticus	Associated with gastroenteritis and IBD; also found in oral, perianal, and soft tissue abscesses, soft tissue or bone infections, and ulcers or gangrenous lesions of the lower limb

[a] No disease association in humans has been reported for *C. avium*, *C. canadensis*, *C. corcagiensis*, *C. cuniculorum*, *C. lanienae*, *C. lari* subsp. *concheus*, *C. peloridis*, *C. subantarcticus*, *C. troglodytis*, *C. volucris*, "*Campylobacter* sp. Dolphin DP," and "*Campylobacter* sp. Prairie Dog" (as of December 2014).
[b] Includes *C. fetus* subsp. *fetus*, *C. fetus* subsp. *venerealis*, and *C. fetus* subsp. *testudinum*.
[c] The table was updated from the work of Man (1).

80% of patients reporting diarrhea that lasted 14 days or more, whereas only 32% of those infected with *C. jejuni* or *C. coli* reported prolonged diarrhea (23). Similar to the case profile for *C. concisus* infection, infection with *C. fetus* is more common than infection with *C. jejuni* and *C. coli* in older patients (68.4 years versus 28.6 years) (12).

Epidemiology

There is evidence to suggest that there has been a rise in the global incidence of campylobacteriosis in the past decade. The numbers of cases of campylobacteriosis have increased in North America, Europe, and Australia. Although epidemiological data from Africa, Asia, and the Middle East are still incomplete, these data indicate that *Campylobacter* infection is endemic in these regions. Differences in the incidence and number of cases reported from different countries or regions within the same country may vary substantially (Fig. 2) (25, 26). It is likely that these variations arise, in part, from differences in the sensitivity of detection methodologies and the area, population, and scope of the case profile studied, as well as differences in the standard and stringency of biocontrol protocols, surveillance bias, food practices, and availability of natural reservoirs for *Campylobacter* species in these regions. Furthermore, the reported cases of *C. jejuni* and *C. coli* infections are likely to represent only the tip of the iceberg owing to underreporting (27).

An additional factor that has been hypothesized to influence the prevalence of *Campylobacter* infections is population-level immunity (28). Population-level immunity refers to the host immune response against an infection within a population that can provide protection against transmission of an infection and/or disease for unprotected individuals. At the population level, this can have impacts on the epidemiology and risk assessment of campylobacteriosis (28). In developing countries where *Campylobacter* is endemic, infection is usually limited to children, with illness/infection ratios decreasing with age, suggesting that exposure in early life might lead to the development of protective immunity (13). This might reflect why asymptomatic *Campylobacter* infections are common in developing nations, which could also have an impact on the transmission of *Campylobacter* infections in these regions due to asymptomatic excretion (28). Asymptomatic excretion is also found in developed countries, with a number of studies showing that a majority of shedders are asymptomatic (29, 30).

Outbreaks caused by *Campylobacter* species are not uncommon. The Centers for Disease Control and Prevention defines a foodborne disease outbreak as the occurrence of more cases than expected in a particular area or among a specific group of people during a specific period, usually with a common cause. Since 2007, the numbers of individuals reported in published outbreaks of campylobacteriosis have ranged from 10 to more than 100 and have correlated with the type of event and environmental source of infection (Fig. 3). The most common reported sources of *Campylobacter* responsible for outbreaks are consumption of poultry products or water (Fig. 3). Between 1992 and 2009, 143 outbreaks were reported in England and Wales, United Kingdom. Of these, 114 were due to contaminated food or water, 2 to animal contact, and 22 to an unknown mode of transmission (31). According to records from the Centers for Disease Control and Prevention, there were 4,936 *Campylobacter* outbreaks in the United States between 1999 and 2008 (32). Between 2009 and 2010, 56 confirmed and 13 suspected outbreaks were reported to the U.S. National Outbreak Reporting System, among which 1,550 illnesses

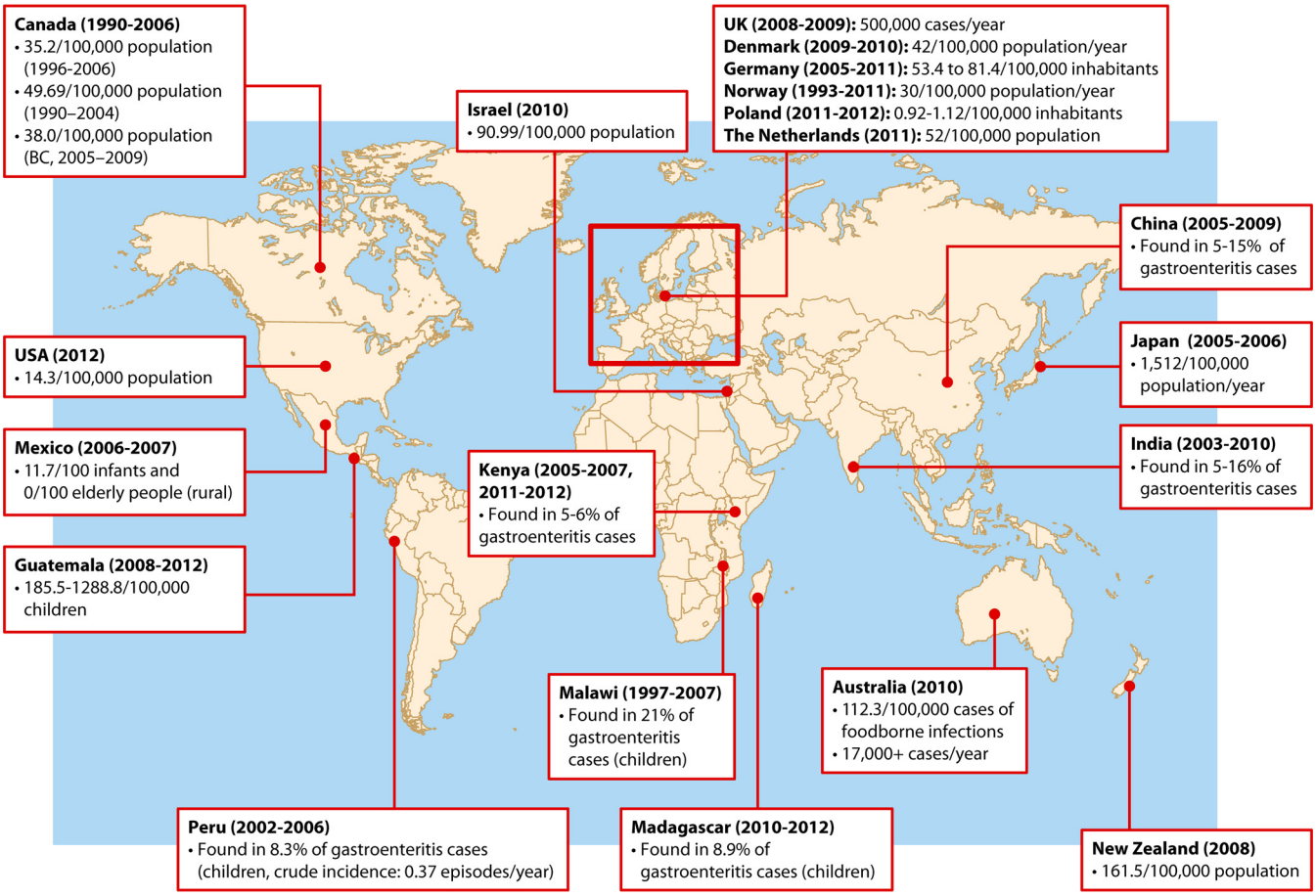

FIG 2 Incidence and prevalence of campylobacteriosis (*C. jejuni*/*C. coli*). The latest information on the global epidemiology of campylobacteriosis from the literature is shown, including data from the United Kingdom (47), Denmark (11), Germany (49), Norway (424), Poland (25, 50, 425), the Netherlands (51), Israel (67), China (60, 61), Japan (26), India (63–65), Australia (69), New Zealand (73), Madagascar (78), Malawi (77), Kenya (79, 426), Guatemala (41), Peru (427), Mexico (428), the United States (10 sites within The Food-Borne Diseases Active Surveillance Network) (34), and Canada (37–39). B.C., British Columbia. (Map adapted from an image from Wikimedia Commons [http://commons.wikimedia.org/wiki/File:A_large_blank_world_map_with_oceans_marked_in_blue.PNG].)

and 52 hospitalized cases were recorded (33). Unfortunately, outbreak data from developing nations are severely lacking. A full list of published campylobacteriosis outbreaks since 2007 is shown in Fig. 3. Below, we summarize the epidemiological data from different regions of the world.

North and Central America. In the United States, the annual number of campylobacteriosis cases, based on 10 years of outbreak data (1998 to 2008), was estimated to be 845,024 cases, resulting in 8,463 hospitalizations and 76 deaths (32). The U.S. Food-Borne Diseases Active Surveillance Network (1996 to 2012) reported an annual incidence of 14.3 per 100,000 population for *Campylobacter* infection (34). Batz and colleagues estimated the annual costs of campylobacteriosis to be $1.7 billion in the United States (35). Importantly, there was a 14% increase in the incidence of campylobacteriosis in 2012 compared to the 2006–2008 period, whereas the incidences of *Cryptosporidium*, *Listeria*, *Salmonella*, *Shigella*, Shiga-toxigenic *Escherichia coli* (STEC) O157, and *Yersinia* infections decreased over the same period (34). Analysis of seven states in the United States within the Food-Borne Diseases Active Surveillance Network revealed that of nine common foodborne pathogens, *Campylobacter* was the leading cause of travel-associated gastroenteritis from 2004 to 2009, accounting for 41.7% of cases (3,445 of 8,270 cases reported), followed by *Salmonella* (36.7%) and *Shigella* (13.0%) (36). The same study also found that *Campylobacter* species were the second most prevalent pathogens in non-travel-associated gastroenteritis, behind *Salmonella* species, accounting for 26.5% of the 14,782 cases reported between 2004 and 2009 (36).

In Quebec, Canada, 28,521 cases of campylobacteriosis were reported between 1996 and 2006, which yielded an estimated annual incidence of 35.2 cases per 100,000 persons (37). A higher incidence of campylobacteriosis (49.69 cases per 100,000 people) was reported from 1990 to 2004 in the Waterloo region of Ontario, Canada (38). In southwestern Alberta, Canada, 36.9% and 5.4% of the patients with diarrhea reported from 31 May to 31 October 2005 were positive for *C. jejuni* and *C. coli*, respectively (14). With a rate among the highest in the country, the province of British Columbia had an annual average of 38.0 cases per 100,000 people during 2005 and 2009 (39).

In Mexico, *C. jejuni* was the most common cause of acute gastroenteritis in infants and preschoolers in 2006 and 2007 (isolated in 15.7% of 5,459 cases) (40). Campylobacteriosis is also very

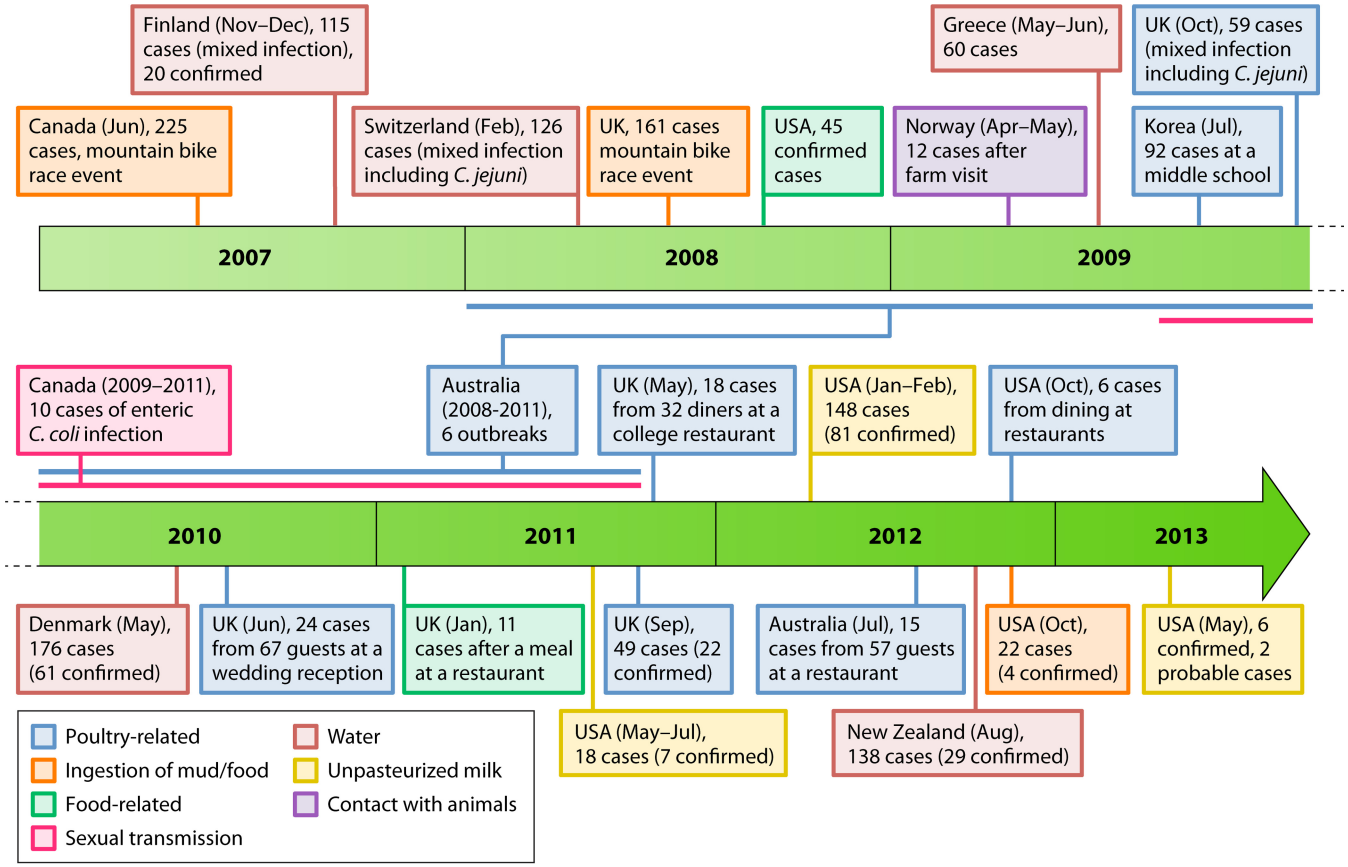

FIG 3 Timeline of published campylobacteriosis outbreaks since 2007 (381, 382, 429–447).

common in children in Guatemala, with incidence rates of 185.5 to 1,288.8 per 100,000 children (41). One study estimated that the incidence of campylobacteriosis in Barbados in 2000 was 5.4 per 100,000 inhabitants—an incidence which had doubled in 2002 (42). However, there is no further report describing the incidence of human campylobacteriosis in this region. Overall, *C. jejuni* is a major pathogen in the United States and Canada, but its precise impact in regions of Central America is less clear.

South America. In 2011, Fernández reviewed the available data on the prevalence of *C. jejuni* and *C. coli* in South America (43). The prevalences of *C. jejuni* ranged from 4.6 to 30.1% of diarrheic patients in Argentina (three studies), while those of *C. coli* were 0 to 1.4%, with *C. coli* being responsible for a third of the *Campylobacter*-related gastroenteritis cases in one of these studies. However, none of these studies included a control group. In Bolivia, the prevalences of *C. jejuni* ranged from 4.4 to 10.5%; however, of the two studies cited, one included a control group in which *C. jejuni* was detected in 9.6% of the controls. Similarly, two studies in Brazil found that the levels of detection of *C. jejuni* were similar between patients (5.8 to 9.6%) and controls (4.9 to 7.2%), while those of *C. coli* ranged from 2.2 to 6.0% for patients and from 1.2 to 2.0% for controls. Detection levels of *C. jejuni* and *C. coli* in gastroenteritis patients ranged from 0 to 14.1% in Chile, 0 to 14.4% in Colombia, 0 to 23.0% in Ecuador, 0.6 to 18.4% in Paraguay, 0 to 23.0% in Peru, 0 to 14.3% in Uruguay, and 0 to 13.0% in Venezuela (43).

In 2013, Collado and colleagues reported the detection of *C. jejuni* and emerging *Campylobacter* species in patients with gastroenteritis from southern Chile (44). In this study, fecal samples were collected from participants over the period from November 2010 to March 2012, and the presence of *Campylobacter* species was detected by PCR. Of the 140 patients, 11.4% tested positive for *C. concisus* DNA, compared to only 3.4% of the 116 healthy controls ($P < 0.05$) (44). Notably, the prevalence of *C. concisus* DNA in gastroenteritis patients was found to be similar to that of *C. jejuni* (10.7%). In Peru, a study that included 150 pediatric stool samples from the Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort study detected *C. jejuni*/*C. coli* in 41.3% of the children with gastroenteritis and 18.7% of the controls ($P = 0.007$) (45). In contrast, the difference in the prevalences of other *Campylobacter* species, including *C. hyointestinalis* subsp. *lawsonii*, *C. troglodytis*, and *C. upsaliensis*, in children with gastroenteritis (33%) and in controls (24%) was not statistically significant (45). Taken together, the data from South America indicate that *Campylobacter* species contribute to the etiology of gastroenteritis, but the contribution of campylobacteriosis to this disease, relative to the contributions of other major pathogens, is unclear.

Europe. The most current evaluation of the epidemiology of campylobacteriosis in 27 European Union (EU) state members indicated the incidences of *Campylobacter* infections to range from 29.9 to 13,500 per 100,000 population in 2009 (with the lowest incidences in Finland and Sweden and the highest in Bul-

garia) (46). Overall, this equated to 9.2 million cases, compared to 6.2 million cases of salmonellosis, in 2009 (46). A United Kingdom-wide study conducted over the period from April 2008 to August 2009 identified *Campylobacter* species as the most common bacterial pathogens in cases of gastroenteritis (47). In this study, the reported rate of campylobacteriosis was 9.3 cases per 1,000 person-years in the community, with an estimated total of 500,000 cases and 80,000 general practitioner consultations across the United Kingdom annually (47). Investigation of the prevalence of pathogen-induced diarrhea in the United Kingdom in 2008 to 2009 revealed that the prevalence of *Campylobacter* species had not decreased compared to that observed 15 years prior (21). In contrast, the prevalences of enteroaggregative *E. coli*, *Salmonella*, and *Yersinia enterocolitica* had all decreased over the same 15-year period (21).

Similarly, in Germany, the prevalence of campylobacteriosis in 2011 was similar to the data from 2001; in contrast, over the same period, the prevalence of salmonellosis had decreased (48). In 2011, there were 70,560 reported cases of campylobacteriosis, a prevalence higher than that reported for *Salmonella*, *Shigella*, *Yersinia*, and *Listeria* infections (48). According to data from Hesse, Germany, the annual incidences of campylobacteriosis between 2005 and 2011 ranged from 53.4 to 81.4 cases per 100,000 persons (49). While in Poland the estimated incidence in 2012 was reported to be 1.12 cases per 100,000 inhabitants, it is likely that campylobacteriosis is underdiagnosed and underreported in this region (25, 50). Interestingly, a study from the Netherlands predicted that in 2060 the incidence of campylobacteriosis in this region will be similar to that in 2011, at 51 per 100,000 population (51). The same model estimated that salmonellosis would account for only 12 cases per 100,000 persons in 2060. However, it is important that these estimates were calculated using age-specific demographic forecasts for 10-year periods between 2020 and 2060, without having considered other factors, such as social clustering, health care systems, and food processing and preparation. Altogether, the estimated cost of illness in the Netherlands due to campylobacteriosis was €21 million per year (52). The high levels of campylobacteriosis across Europe may be reflected in the continuous increase in the number of *C. jejuni*-related GBS cases in Paris between 1996 and 2007 (mean annual increment, 7%; $P = 0.007$) (53).

Epidemiological data from Europe over the last 3 years have transformed our understanding of the clinical importance of emerging *Campylobacter* species in health and disease. Data collected from the Netherlands between March and April 2011 revealed that 71.4% of 493 gastroenteritis cases were PCR positive for *Campylobacter* DNA, among which 20 were *C. jejuni*-associated cases (4.1%). In addition, a further subset of samples was sequenced, which allowed the identification of other *Campylobacter* species, including *C. concisus* (4.1%), *C. concisus* or *C. curvus* (0.8%), *C. ureolyticus* (0.6%), *C. gracilis* (0.6%), *C. showae* or *C. rectus* (0.4%), *C. upsaliensis* (0.4%), *C. hominis* (0.2%), and *C. sputorum* (0.2%) (54). These results suggest that, in the Netherlands, the prevalence of *C. concisus* in gastroenteritis is similar to that of *C. jejuni*. A similar finding based on a culture-dependent approach has been reported for Denmark, where the prevalences of *C. jejuni* and *C. concisus* in adults and children were comparable, with the annual incidence of *C. concisus* infection reported to be 35 cases per 100,000 inhabitants in 2009 and 2010 (11, 55). This is in line with results from Portugal, where *Campylobacter* species were detected in 31.9% of diarrheic fecal samples, with *C. jejuni* and *C. concisus* being the most prevalent species (13.7% and 8.0%, respectively) (56). Furthermore, based on PCR analysis, the prevalences of *C. ureolyticus* in gastroenteritis cases in Ireland in the period from 2009 to 2012 ranged from 1.15 to 1.30% (57, 58). Furthermore, molecular screening for seven members of the *Campylobacter* genus by using PCR revealed the overall prevalence of *Campylobacter* species in patients with gastroenteritis from southern Ireland to be 4.7%, with *C. jejuni* being the predominant species, accounting for 66% of all *Campylobacter* species detected, followed by *C. ureolyticus* (22.3% of all *Campylobacter* species detected), *C. coli* (6.7%), *C. fetus* (2.1%), *C. hyointestinalis* (1.3%), *C. upsaliensis* (1.1%), and *C. lari* (0.5%) (59). Overall, there is compelling evidence from Europe to suggest that in addition to *C. jejuni*, emerging *Campylobacter* species contribute to the etiology of gastroenteritis in this region.

Asia and the Middle East. Epidemiological data on campylobacteriosis in Asia and the Middle East are limited. Investigation of the etiology of gastroenteritis in three hospitals in Yangzhou, China, between July 2005 and December 2006 showed that 4.84% of 3,061 patients with diarrhea were PCR positive for *C. jejuni*, with the highest prevalence being detected in those younger than 7 years of age (60). Between 2005 and 2009, 14.9% (142/950 patients) of patients with gastroenteritis in a hospital in Beijing, China, were reported to be positive for *Campylobacter* species (127 with *C. jejuni* and 15 with *C. coli*) (61). Based on detection rates of *Campylobacter* in raw chicken and the consumption trend of chicken products in China from 2007 to 2010, Wang and colleagues predicted that 1.6% of the urban and 0.37% of the rural population are affected by campylobacteriosis every year (62). In the Miyagi Prefecture of Japan, Kubota and colleagues estimated that, from 2005 to 2006, the numbers of acute gastroenteritis episodes associated with *Campylobacter*, *Salmonella*, and *Vibrio parahaemolyticus* infections were 1,512, 209, and 100 per 100,000 population per year, respectively (26), suggesting that *Campylobacter* species are responsible for the majority of bacterial gastroenteritis cases in this region. The unusually high incidence of campylobacteriosis in this region may be attributed to a range of factors, such as unexpected outbreaks during the time frame examined and/or the methodologies used to estimate the incidence rate. Nevertheless, the high incidence of campylobacteriosis in certain regions of Asia highlights the need for further active surveillance of food safety.

In India, recent data from an infectious disease hospital in Kolkata reported that, in the period from January 2008 to December 2010, 7.0% (222/3,186 patients) of hospitalized patients with gastroenteritis were culture positive for *Campylobacter* species, with 70% of the isolates identified as *C. jejuni* (63). Based on real-time PCR analysis, Sinha and colleagues reported 16.2% (11/68 samples) of diarrheic stool samples from patients in the same region to be positive for *Campylobacter* species (64). Campylobacteriosis has also been reported to be most prevalent in children under the age of 5 years in this region (isolated in 10% of cases, compared to 3.7% for other age groups; $P < 0.001$) (63). In Vellore, South India, between January 2003 and May 2006, 4.5% of 349 children under the age of 5 years with diarrhea were positive by PCR for *C. jejuni* or *C. coli* (65). In addition, in a prospective case-control study conducted between 1 December 2007 and 3 March 2011 to identify the etiology of diarrhea in children aged 0 to 59 months, *C. jejuni* was reported to be significantly associated

with moderate to severe diarrhea in children from Kolkata, India, Mirzapur, Bangladesh, and Karachi, Pakistan (66). However, a further study that examined 144 Bangladeshi children failed to identify a significant association between *Campylobacter* species, including *C. jejuni*/*C. coli*, *C. troglodytis*, *C. hyointestinalis* subsp. *lawsonii*, *C. concisus*, and *C. upsaliensis*, and diarrhea (45).

The most recent data from the Middle East show *Campylobacter* species to be a major and increasing cause of gastroenteritis in this region. For example, the annual incidence of campylobacteriosis in Israel increased from 31.04 cases per 100,000 population in 1999 to 90.99 cases per 100,000 population in 2010, with children under the age of 2 years having the highest incidence (356.12 cases per 100,000 population) (67). Consistently, a study conducted between 2007 and 2009 showed that of 99 hospitalized children with gastroenteritis reported in a hospital in Nahariya, Israel, 61% were positive for *Campylobacter* species, followed by *Shigella* (24%) and *Salmonella* (16%) (68). It is difficult to accurately assess the burden of *Campylobacter* infections in Asia owing to insufficient epidemiological data. There is nevertheless a trend indicating a possible rise in the incidence of campylobacteriosis in the Middle East.

Oceania. Campylobacteriosis is the most commonly notified foodborne infection in Australia, with 16,968 notified cases (112.3 cases per 100,000 cases of notified foodborne infection) in 2010 (69–71). In 2010, the prevalence of *Campylobacter* infections increased 6% compared with the data from 2008 and 2009 (69–71). Similarly, an increase in salmonellosis notifications was observed, with 11,992 notifications (53.7 cases per 100,000 cases) in 2010, compared to 9,533 notifications (43.6 cases per 100,000 cases) in 2009 and 8,310 notifications (39 cases per 100,000 cases) in 2008 (69–71). In contrast, Gibney and colleagues reported *Campylobacter* to be the second leading cause of acute gastroenteritis in Australia in 2010, after norovirus, with the highest disability-adjusted life-year burden (72).

In New Zealand, over the period from 2002 to 2006, the incidence of campylobacteriosis was reported to be 353.8 cases per 100,000 population. However, in 2008, this high incidence dropped substantially, to 161.5 cases per 100,000 population, due to successful intervention strategies within the poultry sector in this region (discussed further below) (73). Epidemiological data available from 364 patients with campylobacteriosis from New Zealand, obtained through telephone and postal questionnaires, showed that 47% of the cases were due to consumption of contaminated food, 27.7% from direct contact with animals, 6.9% from overseas travel, 3.3% from consumption of contaminated water, and 11% from an unknown mode of transmission (74). A study from New Zealand suggested that emerging *Campylobacter* species are not associated with gastroenteritis cases (75). Among the fecal samples collected in that study, between 2007 and 2009, *C. concisus* (healthy controls, 53.1%; patients, 46.9%), *C. ureolyticus* (healthy controls, 24.5%; patients, 10.9%), *C. hominis* (healthy controls, 16.3%; patients, 8.6%), and *C. gracilis* (healthy controls, 6.1%; patients, 14.1%) were detected in samples from both patients and healthy controls, with similar frequencies (75). However, the authors concluded that given the level of genetic diversity within these species, in particular *C. concisus*, the possibility that they may play a role in disease cannot be ruled out.

Only one study has investigated the prevalence of *Campylobacter* species in the regions of Oceania other than Australia and New Zealand. Howard and colleagues reported the isolation of *Campylobacter* species from 143/1,167 (12%) gastroenteritis cases, compared to 20/660 (3%) controls, among children admitted to the Goroka Base Hospital, Papua New Guinea, between October 1985 and March 1990 (76). More data are required to elucidate the epidemiological landscape of campylobacteriosis in most Oceania regions.

Africa. Data from a limited number of countries in Africa have indicated that *Campylobacter* infection is most prevalent in the pediatric population. A 10-year study (1997–2007) from Blantyre, Malawi, Africa, found that *C. jejuni* and *C. coli* were detected in 21% (415/1,941 children) of hospitalized children with diarrhea by real-time PCR, with *C. jejuni* accounting for 85% of all campylobacteriosis cases (77). Between 1997 and 1999, nondiarrheic children were also examined, and 14% were PCR positive for *C. jejuni* and *C. coli* (77). Although this prevalence was significantly lower than that for children with diarrhea within the same period (28%; $P < 0.001$) (77), these observations indicate that *C. jejuni* and *C. coli* are endemic in this pediatric population. These findings are supported by a study conducted in Moramanga, Madagascar, where the rate of *Campylobacter* isolation from diarrheic samples was reported to be 8.9% (41/459 samples), while that in nondiarrheic samples was 9.4% (278/2,965 samples) (78). In Kenya, samples collected from May 2011 to May 2012 at a hospital in Kisii for the detection of a range of enteric pathogens showed 5.8% (9/156 samples) of samples from patients with diarrhea to be culture positive for *Campylobacter* species, which was significantly higher than the incidence of 0.6% (1/156 samples) in the controls ($P = 0.02$) (79). A further study which described 138 Tanzanian children and the use of diverse detection techniques, including culture, enzyme immunoassay, and PCR, reported the detection of *C. jejuni*/*C. coli* in 34.8% of gastroenteritis cases and 30.4% of controls and other, non-*jejuni*/*coli Campylobacter* species in 47.8% of gastroenteritis cases and 42.0% of controls (45). These differences, however, did not reach statistical significance (45). Pioneering work conducted by Lastovica and colleagues in South Africa, who used culture methods optimal for the isolation of most *Campylobacter* species, unveiled a more complete and realistic epidemiological landscape of *C. jejuni* and emerging *Campylobacter* species. From 2005 to 2009, 5,443 strains of *Campylobacter* species were isolated from stools of children with diarrhea at the Red Cross Children's Hospital in Cape Town. Of these, 40% were *C. jejuni* (32.3% *C. jejuni* subsp. *jejuni* and 7.7% *C. jejuni* subsp. *doylei*), while the second most prevalent organism was *C. concisus* (24.6%) (80). From 1990 to 2009, Lastovica cultivated more than 2,000 clinical isolates of *C. concisus* (81), a valuable collection which could be characterized further by more extensive genomic sequence analyses. Overall, it is not unreasonable to conclude that *C. jejuni* and other *Campylobacter* species are endemic to children in most surveyed regions of Africa.

OTHER GASTROINTESTINAL MANIFESTATIONS

While gastroenteritis is a major clinical condition resulting from *Campylobacter* infection, these organisms have also been associated with a range of other serious conditions within the gastrointestinal tract, including IBD, esophageal diseases, periodontitis, functional gastrointestinal disorders, celiac disease, cholecystitis, and colon cancer. Here we review the epidemiology and impact of *Campylobacter* infection in these gastrointestinal diseases.

Inflammatory Bowel Diseases

IBD are chronic inflammatory conditions of the gastrointestinal tract which include Crohn's disease (CD) and ulcerative colitis (UC). The phenotype in patients with CD is characterized by transmural lesions that may occur in any site along the gastrointestinal tract, while patients with UC are affected by continuous submucosal inflammation restricted to the colon. Despite extensive research, the etiology of IBD has yet to be elucidated; however, the general hypothesis is that they are complex diseases in which a dysregulated immune response that leads to chronic inflammation arises as a result of a dysregulated gastrointestinal microbial ecology, host genetic factors, and a disruption of the gastrointestinal epithelium triggered by environmental factors (82).

The role of *Campylobacter* species in IBD has been investigated for the past 3 decades. *C. jejuni* was the initial focus of research (83–85), but it was not until 2009 that Gradel and colleagues provided evidence that indicated an association between *C. jejuni* infection and an increased risk of IBD (86). Furthermore, recent studies investigating the role of other emerging *Campylobacter* species in IBD have provided solid evidence that demonstrates an association between *C. concisus* and these gastrointestinal disorders (81, 87–94).

The association between emerging *Campylobacter* species (*C. concisus*, *C. showae*, *C. hominis*, *C. gracilis*, *C. rectus*, and *C. ureolyticus*) and CD was first described by the Mitchell group in 2009 (87). For a cohort of newly diagnosed pediatric CD patients, 82% of intestinal biopsy specimens were found to be positive for *Campylobacter* DNA by PCR, compared to 23% of control samples (87). Only the prevalence of *C. concisus* DNA was found to be significantly higher in patients with CD (51%) than in controls (2%) ($P < 0.0001$) (87). Consistent with this, a study by Tankovic and colleagues found that *C. concisus* was present in 21% (4/19 patients) of IBD patients but only 9% (1/11 controls) of controls (88). In 2010, Man and colleagues further reported that 65% of fecal samples from patients with CD were positive for *C. concisus*, compared to 33% of samples from healthy controls and 37% of samples from non-IBD controls, and the differences were statistically significant ($P = 0.03$ and $P = 0.008$, respectively) (89). Further analyses to investigate the fecal microbiota in a subset of these patients by using pyrosequencing techniques detected *C. concisus* in two CD samples but not in controls, which indicates that *C. concisus* DNA was present in sufficient quantity to be detected by less sensitive approaches (90). The increased prevalence of *C. concisus* DNA in CD patients compared to controls appears to be specific to the intestinal tract, because no difference in prevalence of *C. concisus* DNA was found for saliva samples from IBD patients (100%; 13 CD patients and 5 UC patients) and healthy controls (97%; 57/59 controls) (95). This raises the possibility that the oral cavity may be a natural reservoir for *C. concisus*.

In a study to investigate whether specific microorganisms were selectively transported to the lymph nodes of CD patients, O'Brien and colleagues used high-throughput sequencing and reported *Campylobacteraceae* DNA to be present in three CD patients (96). In line with this, a study by Kovach and colleagues identified 37 immunoreactive proteins of *C. concisus*, detected using sera collected from 10 *C. concisus*-positive children with CD (97). Of these proteins, flagellin B, the ATP synthase F1 α subunit, and outer membrane protein 18 were consistently recognized by all CD patients (97).

Similarly, the prevalence of *C. concisus* was reported to be higher in patients with UC (91–94). For example, Mahendran and colleagues found a higher prevalence of *C. concisus*, not only in colonic biopsy specimens from adult CD patients (53%; 8/15 patients) but also in those from UC patients (31%; 4/13 patients), than in controls (18%; 6/33 individuals) ($P < 0.05$) (91). Two further studies, conducted in Scotland, showed an increased prevalence of *C. concisus* DNA in both adults and children presenting with UC (92, 93). The first study isolated *C. concisus* from three children with IBD (two with CD and one with UC) but not from any of the controls; however, based on PCR, the prevalences of *C. concisus* were not significantly different between patients and controls (92). In contrast, the second study detected a significantly higher prevalence of *C. concisus* DNA (33.3%; 23/69 samples) in intestinal biopsy specimens from adult UC patients than in controls (10.8%; 7/65 individuals) ($P = 0.0019$) (93). More recently, Rajilic-Stojanovic and colleagues examined the fecal microbiota of 15 UC patients during remission and 15 controls, using a highly reproducible phylogenetic microarray assay that can detect and quantify more than 1,000 intestinal bacteria in a wide dynamic range. This showed the levels of *Campylobacter* and other pathogens (*Fusobacterium*, *Peptostreptococcus*, and *Helicobacter*) to be increased in the fecal samples from UC patients compared with those in controls ($P = 0.0004$) (94). The reason for the increased level of *Campylobacter* species during the remission stage of UC is unclear, and the identity of the *Campylobacter* species is unknown, as only the genus information was provided (94).

Despite solid evidence supporting an association between *C. concisus* and IBD, the observation that *C. concisus* is detected in the intestines of one-third of cohorts without IBD raises the possibility that *C. concisus* may simply be present as a result of dysbiosis and intestinal inflammation (1, 98). Although causality between *C. concisus* and IBD has not yet been established, recent studies have focused on identifying specific genetic variants of *C. concisus* or genomospecies that may be associated with disease. *C. concisus* is a genetically heterogeneous species which is defined by 2 to 4 genetically variable genomospecies (99–105). A recent study by our group addressed this issue by determining the levels of *C. concisus* exotoxin 9/DnaI, a putative virulence factor postulated to be associated with increased survival in the cell, in patients with CD (106–108). This showed exotoxin 9/DnaI levels to be significantly higher in fecal samples from CD patients [48.8 ± 20.7 pg (g feces)$^{-1}$] than in controls [4.3 ± 1.1 pg (g feces)$^{-1}$] ($P = 0.037$). Based on these findings, it is possible that IBD patients are colonized by strains harboring specific virulence factors (106). Furthermore, our group also identified the zonula occludens toxin (Zot) gene within the genomes of some *C. concisus* strains (109), and we showed that the levels of Zot gene DNA in patients with moderate to severe CD were increased compared to those for mild CD [for mild CD, 1.6 ± 0.7 pg (g feces)$^{-1}$; and for moderate/severe CD, 4.4 ± 1.0 pg (g feces)$^{-1}$] ($P = 0.059$) (110). Based on these and other findings on the pathogenicity and immunogenicity of *C. concisus* (108, 111, 112), we hypothesized that *C. concisus* strains can be subdivided into the following two pathotypes which differ from nonpathogenic strains: (i) adherent and invasive *C. concisus* (AICC), which possesses a superior ability to survive intracellularly within host cells (potentially involving exotoxin 9/DnaI and other virulence factors); and (ii) toxigenic *C. concisus* (AToCC), which produces Zot, with the potential to target tight

junctions of host cells (98). Further characterization of the prevalence of these strains in IBD is required.

In addition to *C. concisus*, Mukhopadhya and colleagues found 21.7% (15/69 samples) of samples from UC patients and 3.1% (2/65 samples) of samples from controls ($P = 0.0013$) to be PCR positive for *C. ureolyticus* (93). Overall, further investigations are required to establish a causative role; nevertheless, these findings collectively indicate an important contribution of *C. concisus* to the pathogenesis of IBD.

Esophageal Diseases

Esophageal diseases include gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal adenocarcinoma. GERD is a chronic disorder in which mucosal damage to the esophagus occurs due to stomach acid or, occasionally, stomach content, which may contain bile, flowing back into the esophagus, which over time increases the risk of BE. In turn, BE is a preneoplastic condition defined by the replacement of normal squamous mucosa by metaplastic columnar mucosa in the distal esophagus. This event increases the predisposition to the development of esophageal adenocarcinoma.

Early studies have reported the bacterial composition to differ in individuals with a healthy esophagus, GERD, and BE. The bacterial communities detected in these sites are primarily characterized by members of four phyla: the *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* (113–118). Recent studies have demonstrated that *Campylobacter* species, and *C. concisus* in particular, are among the dominant species present in patients with GERD and BE (113, 119). For example, in a study by Macfarlane and colleagues which examined the presence of aerobic, microaerobic, and anaerobic microorganisms in esophageal aspirates and mucosal samples from patients with BE, 57% of patients were reported to be colonized by *Campylobacter* species, the majority of which were *C. concisus* (113). In agreement with these findings, Blackett and colleagues reported *Campylobacter* species, almost exclusively *C. concisus*, to be increased in patients with GERD and BE, but not in esophageal adenocarcinoma patients, compared with healthy controls (119). This finding suggests a possible association between *C. concisus* colonization and reflux into the esophagus. Furthermore, the authors showed a strong correlation between *C. concisus* colonization and production of interleukin-18 (IL-18) (119), a cytokine that stimulates both innate and adaptive immune responses and has been widely associated with carcinogenesis (120).

Periodontal Diseases

C. rectus, *C. gracilis*, *C. showae*, and *C. concisus* have been identified as potential oral pathogens, while other *Campylobacter* species, including *C. curvus*, *C. sputorum*, and *C. ureolyticus*, have been isolated from the oral cavity; however, it remains unclear if they are linked to periodontal disease (1, 121–129). Gingivitis is a preventable and reversible clinical condition that includes erythema, edema, bleeding, sensitivity, tenderness, and enlargement. Periodontitis is a more severe condition characterized by a loss of clinical attachment level, reduction in bone level, and, ultimately, tooth loss. These oral inflammatory conditions are induced by biofilms that accumulate in the gingival margin and are reported to be initiated in periodontal tissue by a number of bacterial species, including *C. rectus* (121).

A number of studies have shown *C. rectus* to be associated with higher levels of clinical attachment loss, bleeding on probing of the sampled site, and probing depth (121, 130–133). Furthermore, the abundance of *C. rectus* has been reported to be elevated significantly in patients with chronic gingivitis and moderate periodontitis but not in severe periodontitis patients, suggesting that this organism is associated with the early stages of periodontitis (130, 134). *C. gracilis* has been isolated from the oral cavities of individuals presenting with dental caries (135–137), and its reported coaggregation with *Actinomyces* species has led to the suggestion that these Gram-negative obligate anaerobic rods contribute to the development of biofilms, dental plaque, and root caries (138).

Evidence that *C. showae* and *C. concisus* may also play a role in periodontal disease has been reported in a number of studies. For example, an increased prevalence and abundance of both species have been observed at active periodontal disease sites (121, 128, 129, 139–141). Furthermore, the findings that substantially increased levels of *C. concisus* are observed at periodontal sites with a more severe gingival bleeding index and that the presence of a systemic humoral immune response against *C. concisus* can be observed in patients with periodontal disease support the view that this species is an oral pathogen (142–144). In contrast, one study observed reduced levels of *C. showae* in plaque from white-spot or dentin lesions of patients with periodontal disease compared with the levels in healthy subjects (135), while another reported that *C. concisus* was associated with an increase in tooth attachment in a patient with periodontitis (145).

It has been speculated that oral colonization by *Campylobacter* species may lead to other pathological consequences in the body. For example, a study by Ercan and colleagues suggests that the presence of *C. rectus* in the oral cavity of pregnant women with periodontal disease may lead to adverse pregnancy outcomes, including preterm birth and low birth weight (146). Furthermore, this observation was reported to be more pronounced in those with generalized periodontitis and a high bleeding index. Whether this phenomenon relates to the ability of bacteria and their products to diffuse more readily when vascular permeability increases in gingival tissues during pregnancy remains to be determined. A small number of studies have investigated a possible etiological association between oral *Campylobacter* species and IBD. It is interesting that periodontal disease and IBD share some common clinical features and are both associated with an unusual microbiota. For example, levels of *C. gracilis* have been reported to be significantly higher at periodontitis sites of patients with CD than at those of patients with UC or than the levels in healthy controls (147). In addition, elevated levels of *C. concisus* can be found in periodontal lesions of IBD patients, and the oral cavity in these patients may be colonized by specific orally affiliated and enterically invasive *C. concisus* strains (148, 149).

Functional Gastrointestinal Disorders

C. jejuni and other *Campylobacter* species are associated with the development of foodborne gastroenteritis-associated sequelae, including postinfectious functional gastrointestinal disorders (PFGD). Two PFGD have received the most attention: irritable bowel syndrome (IBS) (150–156) and functional dyspepsia (FD) (156–161). IBS is defined by recurrent abdominal pain or discomfort during at least 3 days/month in the last 3 months, associated with an alteration of bowel habits (diarrhea, constipation, or both), in accordance with the Rome III classification system (162). FD is characterized by persistent or recurrent symptoms (pain or

discomfort centered in the upper abdomen) in the last 3 months, in the absence of organic disease (including on upper endoscopy). The postinfectious forms of these disorders develop *de novo* despite clearance of the causative agent.

The mechanisms underlying postinfectious IBS are poorly understood but might include persistent changes in the gut microbiota as well as in mucosal immunocytes, enterochromaffin cells, mast cells, and enteric nerves (163). In addition, host factors, including female gender, depression, hypochondriasis, smoking, adverse life events in the preceding 3 months, and treatment with antibiotics, are risk factors for the development of postinfectious IBS (163).

The percentages of individuals presenting with gastroenteritis who develop postinfectious IBS range from 3.7% to 36% (163); however, studies exclusively investigating *C. jejuni*-associated postinfectious IBS showed percentages ranging from 9.0 to 13.8% (152, 164). Furthermore, long-term follow-up studies have revealed that *C. jejuni*-associated postinfectious IBS symptoms can persist for up to 10 years after the infectious event (165, 166). Current evidence suggests that both bacterial and host factors play a crucial role in the predisposition to *C. jejuni*-associated postinfectious IBS. These include increased cytotoxic virulence of the *Campylobacter* strain and increased transcellular bacterial translocation, a reduced absorptive capacity of the gut, and increased mucosal permeability in the host during acute gastroenteritis (167). Experimental evidence that *Campylobacter* toxins are important determinants for the development of chronic gastrointestinal symptoms following acute gastroenteritis comes from a study by Thornley and colleagues, who observed that *Campylobacter* strains associated with postinfectious IBS were more toxigenic to both HEp-2 and African green monkey kidney epithelial (Vero) cells (164). Further studies have shown that *C. jejuni* infection is the strongest risk factor for postinfectious IBS compared to *Salmonella* and Epstein-Barr virus infections (150, 151).

More recently, other *Campylobacter* species have been identified to play a role in postinfectious IBS. Nielsen and colleagues reported patients infected with *C. jejuni*, *C. coli*, and *C. concisus* to be more likely to develop IBS symptoms at 6 months postinfection (23). In a follow-up study, they assessed the risk of postinfectious IBS associated with *C. concisus* and found that patients with gastroenteritis associated with *C. concisus* carried a 25% risk of developing IBS (168).

Similar to the case for IBS, a number of studies have provided evidence for an association between *Campylobacter* infection and a risk of postinfectious FD. A meta-analysis of 19 studies found that following infections with several pathogens, including *C. jejuni*, *Salmonella* spp., *Escherichia coli* O157, *Giardia lamblia*, and norovirus, the prevalences of postinfectious FD were 9.6 and 30.5% in adults and children, respectively (157). Consistent with these findings, Ford and colleagues reported the odds ratio (OR) of postinfectious FD to be 2.30 (95% confidence interval [CI], 1.63 to 3.26) in a cohort study following a waterborne outbreak of infections with *Campylobacter* species and *E. coli* O157 (158). In addition, a recent study by Porter and colleagues reported the relative risk of *Campylobacter*-associated FD among active-duty U.S. military personnel with acute gastroenteritis from 1998 to 2009 to be 2.0 (95% CI, 1.3 to 3.0) (159). Of particular interest, *Campylobacter* species and *E. coli* O157 can be identified in blood tests and stool cultures from postinfectious FD patients (157). Overall, there is good evidence to suggest a link between *Campylobacter* infection and IBS or FD.

Colorectal Cancer

Increasing evidence indicates that dysbiosis of the gut microbiota contributes to the development of colorectal cancer. Currently, due to a lack of epidemiological studies, evidence supporting a role for *Campylobacter* species in colorectal cancer is very limited. However, a recent study by Warren and colleagues, investigating metatranscriptome data obtained from colorectal cancer and control tissues, demonstrated that *Campylobacter* species, predominantly *C. showae*, coaggregate with *Fusobacterium* and *Leptotrichia* species (169). This finding is of particular interest because previous studies have shown that *Fusobacterium* species are overrepresented in colorectal tumors compared to control specimens (170, 171). As part of their study, Warren and colleagues isolated a novel *C. showae* strain (CC57C) from colorectal cancer tissue, which they showed harbored a number of potential virulence genes, including a VirB10/D4 type IV secretion system. Furthermore, *in vitro* assays showed that this strain aggregates with another tumor strain of *Fusobacterium nucleatum* (CC53) (169). Based on these findings, Warren and colleagues raised the possibility that a Gram-negative anaerobic bacterial population comprising *Campylobacter* and *Fusobacterium* might be associated with colorectal cancer (169). Consistent with this, a study by Wu and colleagues (172) which used culture-independent pyrosequencing and reverse transcription-quantitative PCR (RT-qPCR) reported a specific microbial profile, characterized by significant increases in *Bacteroides*, *Enterococcaceae*, *Fusobacterium*, and *Campylobacter* species, to be associated with colorectal cancer. Although these studies provide an indication that *Campylobacter* species are present in patients with colorectal cancer, further studies will be required to determine if any relationship between *Campylobacter* and the development of colorectal cancer exists.

Celiac Disease

Celiac disease is a digestive disorder in which the immune system reacts abnormally to gluten, resulting in damage to the lining of the small intestine. Celiac disease is estimated to affect approximately 1% of people worldwide (173, 174), and the incidence of this disease has increased up to 5-fold in some countries, including the United States (175). In 2007, a case study described for the first time the development of celiac disease in a young healthy woman following infection with *C. jejuni* (176). More recently, Riddle and colleagues reviewed the U.S. Department of Defense medical encounter database to identify whether there is a risk of developing celiac disease following foodborne infection (177). They found that the rates of celiac disease were similar in those with prior diarrhea caused by bacteria (0.07 per 100,000 person-years) and matched controls (0.04 per 100,000 person-years). However, persons diagnosed with campylobacteriosis had a 3.5-fold higher rate of celiac disease (0.15 per 100,000 person-years) than unexposed individuals (177). Furthermore, no patients exposed to any of the other gastrointestinal pathogens, including *Salmonella* (nontyphoidal), *Shigella*, and *Y. enterocolitica*, developed celiac disease (177). To date, there are insufficient epidemiological data to conclude whether campylobacteriosis is associated with celiac disease.

Cholecystitis

Cholecystitis refers to inflammation of the gallbladder that usually arises when the cystic duct is blocked by gallstones, leading to the

accumulation of bile within the gallbladder. *C. jejuni* has been implicated in the development of cholecystitis; however, this is considered rare given that only 15 cases have been described in the literature over the last 30 years (178). One possible reason for this is that the standard conditions used for culture of bacteria from bile samples do not generally favor the growth of *Campylobacter* species; thus, some cases of *Campylobacter*-associated cholecystitis may have been overlooked (178).

EXTRAGASTROINTESTINAL MANIFESTATIONS

In addition to gastrointestinal infection, *Campylobacter* species also cause a range of clinical manifestations in other parts of the body, as either a local isolated infection, a systemic manifestation after an episode of enteritis, or a postinfectious immune disorder. These manifestations include Guillain-Barré syndrome, Miller Fisher syndrome, brain abscesses and meningitis, bacteremia, sepsis, endocarditis and myocarditis, reactive arthritis, and clinical manifestations that result in complications in the reproductive tract. The clinical importance and epidemiology of these extragastrointestinal manifestations as a result of *Campylobacter* infection are discussed in the following sections.

Guillain-Barré Syndrome

GBS was first reported by Landry in 1859 (179, 180); however, it was not until 1916 that the French neurologists Guillain, Barré, and Strohl first described the clinical features of GBS (181). GBS is a neurologic condition characterized by a progressive symmetrical weakness in the limbs, with or without hyporeflexia, which can also affect respiratory and cranial nerve-innervated muscles (180). The two main subtypes of GBS are acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP), with each subtype displaying a distinct immunopathogenesis and response to treatment (182). AMAN is an axonal subtype that progresses more rapidly and is considered the major subtype (30 to 65% of patients) in Asia and Central and South America (182, 183), while AIDP is more prevalent in Europe and North America (182). The annual incidence of GBS is approximately 1.2 to 2.3 cases per 100,000 persons; however, the incidence increases with patient age and male gender (180).

GBS is considered a postinfectious disease, and the major trigger of this disease is *C. jejuni* infection, with a direct correlation between annual rates of GBS and campylobacteriosis being reported. For example, following the implementation of stricter hygiene measures on poultry meat in New Zealand, decreased rates of GBS were observed, which correlated with a fall in the number of campylobacteriosis cases (184). Furthermore, outbreaks of GBS have been associated with outbreaks of *C. jejuni* infection (185). A recent systematic review reported the proportion of *Campylobacter* cases resulting in GBS to be 0.07% (95% CI, 0.03% to 0.15%) (186). Moreover, evidence exists to suggest that the number of *C. jejuni*-related GBS cases is increasing in some countries (53).

The underlying mechanism of the nerve damage associated with GBS is reported to be due to cross-reactivity between antibodies produced in response to *C. jejuni* lipooligosaccharide (LOS) and human gangliosides, such as the GM_1 ganglioside (187). For example, *C. jejuni* strains expressing α2,3-sialylated GD1a/GM1a- and α2,8-sialylated GD1c-mimic LOS structures have been shown to interact with sialoadhesin and sialic acid-binding immunoglobulin-like lectin-7 (Siglec-7), respectively (188, 189). T-cell responses are also important in GBS, with LOS that was α2,8-sialylated being shown to induce Th1 immune responses, while LOS containing α2,3-linked sialic acid induces Th2 responses (188). Evidence of this Th1/Th2 polarized immune response following *C. jejuni* infection comes from a study by Malik and colleagues, who showed that IL-10-deficient mice infected with colitogenic *C. jejuni* had upregulated Th1/17 but not Th2 responses, while GBS-associated *C. jejuni* enhanced Th2 responses but blunted Th1/17 responses (190). Thus, the GBS-associated *C. jejuni* strains may protect against colitis but instead promote autoimmunity. In addition to sialylated LOS structures in *C. jejuni*, two capsule biosynthesis genes (*cj1421c* and *cj1428c*) have been shown to have higher conservation rates among strains isolated from GBS patients than among strains from enteritis patients (191). Furthermore, a gene encoding a glucosyltransferase (*cj1135*) was reported to be more conserved in enteritis strains whose LOS did not mimic gangliosides, suggesting that this gene may function to silence the neuropathogenesis of *C. jejuni* LOS (191).

Miller Fisher Syndrome

Miller Fisher syndrome is a clinical variant of GBS that was discovered in 1956 by Charles Miller Fisher. This condition is defined by acute-onset ophthalmoparesis, areflexia, and ataxia, which arise from the development of anti-GQ1b antibodies following exposure to LOS from certain bacteria (192, 193). Several pathogens have been linked to the molecular mimicry that leads to the development of this condition. Of these, *C. jejuni* is the most frequently identified one (194). Siglec-7 has been shown to exclusively bind to *C. jejuni* strains that express terminal disialylated ganglioside mimics. *C. jejuni* binding to Siglec-7 is reported to correlate with the presence of anti-GQ1b antibodies and oculomotor weakness in patients, suggesting that this may be a potential trigger of Miller Fisher syndrome (195).

In some cases, patients are negative for antibodies against GQ1b (196, 197), indicating that antibodies against gangliosides other than GQ1b may be involved in the development of disease. For example, Oyazato and colleagues reported a recent atypical persistent case of Miller Fisher syndrome following *Campylobacter* enterocolitis where the patient had anti-GA1 antibody in his serum, but not anti-GQ1b and anti-GT1a (198). Further work is required to investigate the etiology and epidemiology of *Campylobacter*-associated Miller Fisher syndrome and the ability of *Campylobacter* species other than *C. jejuni* to trigger this disease.

Bacteremia and Septicemia

One of the most common extragastrointestinal manifestations of *Campylobacter* species is bacteremia, which is predominantly associated with *C. jejuni*, *C. coli*, and *C. fetus* infections (1). At least 10 different *Campylobacter* species have been documented in bacteremia cases, but bacteremia cases associated with *C. lari*, *C. insulaenigrae*, and *C. upsaliensis* infections are rare (1, 80, 199, 200). *Campylobacter*-associated bacteremia cases are often underreported (201). Most cases occur in elderly or immunocompromised patients with one or more concurrent pathologies, including liver cirrhosis or neoplasia; among these patients, 10 to 15% die within 30 days of disease diagnosis (202–204). A recent study conducted in a Danish population reported the estimated incidence of *C. jejuni*-, *C. coli*-, *C. fetus*-, and *C. lari*-associated bacteremia to be 2.9 cases per 1,000,000 person-years, with a peak incidence in patients older than 80 years (205). In contrast, a 10-year nationwide study in Finland concluded that *C. jejuni* and *C. coli*

bacteremias affect predominately younger individuals without major underlying diseases (206). The disease generally results from a single gastroenteritis complication in children or as recurrent episodes in immunocompromised children without gastrointestinal symptoms (207). A number of *Campylobacter* species, including *C. jejuni*, *C. coli*, *C. fetus*, and *C. upsaliensis*, have also been associated with sepsis in both immunocompetent and immunocompromised children and adults (208–210). Furthermore, a number of cases of *C. fetus*-associated neonatal sepsis have been reported (discussed below) (211).

Cardiovascular Complications

Campylobacter species, mainly *C. jejuni* and *C. fetus*, have been detected in association with a wide spectrum of cardiovascular complications, including endocarditis, myocarditis, pericarditis, myopericarditis (pericarditis with concurrent myocardial involvement), atrial fibrillation, and aortitis with aortic dissection.

Myo(peri)carditis (refers to either myocarditis, pericarditis, or myopericarditis) associated with bacterial enteritis is a rare but serious condition in immunocompetent individuals. These conditions can lead to arrhythmia, dilated cardiomyopathy, congestive heart failure, and sudden cardiac death. *Salmonella* and *Shigella* are the main gastrointestinal pathogens linked to myo(peri)carditis, but the increasing incidence of campylobacteriosis worldwide over the last 10 years has drawn attention to *Campylobacter*-associated myo(peri)carditis. Interestingly, Becker and colleagues recently calculated the annual incidence rates of myocarditis, using data obtained from 6,204 individuals with stool cultures positive for *Campylobacter* and 62,040 matched controls, and they found the incidence rate to be 16.1 cases (95% CI, 2.3 to 114.4 cases) per 100,000 person-years in the population with *Campylobacter*-positive stool samples, compared to only 1.6 cases (95% CI, 0.2 to 11.4 cases) per 100,000 person-years in the control population (212). Notably, the same authors did not find a significant difference in the number of myopericarditis cases between the *Campylobacter*-infected and control populations (212). However, because of the rarity of these events (only two cases of myocarditis and two cases of pericarditis were found in the entire study sample), it is important to highlight the low statistical precision of this study.

A number of *C. jejuni*-associated myo(peri)carditis cases have been published since 1980 (213–230). These reports collectively indicate that patients usually present with symptoms such as thoracic pain, with concomitant electrocardiogram changes as well as increased levels of cardiac enzymes, 3 to 5 days after the onset of gastroenteritis. These studies also suggest that males are more susceptible, and microbiological stool cultures and/or serological analyses in these cases reveal *C. jejuni* as the only causative agent. In many cases, blood cultures remain sterile and the outcome is generally benign.

About 11 cases of *C. fetus*-associated myo(peri)carditis have been documented in the English literature. For these cases, blood cultures are generally positive and the outcome is more severe, sometimes even leading to death (225, 231). This might relate to the fact that, in contrast to *C. jejuni*, *C. fetus* tends to cause a more severe compromise of the pericardium, which might be due to colonization of the pericardium following bacteremia and septicemia and might explain the development of nonspecific symptoms, such as fever, malaise, and weight loss (232).

The mechanism by which *Campylobacter* species cause myo(peri)carditis remains unclear. It has been hypothesized that invasion of the cardiac tissue, bacterial exotoxins, circulating immune complexes, and cytotoxic T cells are involved (225). *C. fetus*-associated myo(peri)carditis may also require expression of bacterial surface layer proteins to confer evasion of the host immune system.

Campylobacter-associated endocarditis is an infrequent condition in which both native and prosthetic valves can be affected. Previous studies have shown that individuals with *Campylobacter*-associated endocarditis have either *C. jejuni* or *C. fetus* infection and that one-third of these patients suffer from concurrent chronic diseases, including hepatic cirrhosis, connective tissue disease, tuberculosis, or cancer (233–239). Furthermore, four cases of atrial fibrillation associated with *C. jejuni* infection have been reported in the literature (230, 240), and both *C. jejuni* and *C. fetus* infections have been associated with *Campylobacter*-associated aortitis (241–244). Overall, the limited current evidence suggesting an association between *Campylobacter* species and cardiovascular complications precludes causal inference.

Meningitis

Both *C. jejuni* and *C. fetus* subsp. *fetus* have been implicated in the development of meningitis in humans (245–252). Meningitis caused by *C. fetus* subsp. *fetus* has generally been reported for immunocompromised adults and is rare, with only eight cases reported from 1983 to 1998 (248). *C. jejuni*-associated meningitis is also rare and may affect both healthy and immunocompromised children and adults (246, 247, 251).

Extraoral Abscesses

Campylobacter species have been reported to be present in several types of abscesses outside the oral cavity. *C. rectus* has been associated with a chest wall infection (253), a breast abscess (254), and a vertebral abscess (255), while *C. curvus* has been associated with a liver abscess in a patient with complicated ovarian cancer and a bronchial abscess in a patient with lung cancer (254). *C. gracilis* and *C. concisus* have both been implicated in brain abscesses, while *C. showae* was detected in an intraorbital abscess (255). Most abscesses are polymicrobial in nature, making it difficult to assess the contribution of a specific *Campylobacter* species to the clinical outcome.

Reactive Arthritis

Reactive arthritis is a form of arthritis which most commonly occurs in patients in their 30s or 40s and develops following gastrointestinal or genitourinary infections. This condition can affect joints, such as knees and ankles, as well as the eyes and the genital, urinary, and gastrointestinal systems. Symptoms can begin approximately 1 month following infection and resolve within a year, although in some patients this condition may persist for up to 5 years (256). In 2007, a systematic review by Pope and colleagues reported the incidence of reactive arthritis associated with *Campylobacter* infection to be 1 to 5% (257). Other studies have estimated the risk of reactive arthritis associated with *Campylobacter* infection to be 3 to 13%, compared with 0 to 9% for *E. coli* O157:H7, 2 to 15% for *Salmonella*, 1 to 10% for *Shigella*, and 0 to 14% for *Yersinia* (256). Recently, Ajene and colleagues performed a comprehensive systematic review to identify the global incidence of reactive arthritis associated with infections by enteric pathogens, namely, *Campylobacter*, *Salmonella*, and *Shigella* (258). They

found 25 articles, among which 14 cohort studies were chosen for calculation. Among a total of 63,206 patients infected by *Campylobacter*, 573 developed reactive arthritis, generating an incidence rate of 9 reactive arthritis cases per 1,000 cases of *Campylobacter* infection (258). Furthermore, the incidences of reactive arthritis resulting from *Campylobacter* infection ranged from 8 to 16% in adults and 0 to 6% in children. In comparison, the incidence rate for both *Salmonella* and *Shigella* infections was slightly higher, with 12 reactive arthritis cases per 1,000 infections (258). In a more recent meta-analysis assessing the proportion of *Campylobacter* cases that develop chronic sequelae, Keithlin and colleagues found that only 2.86% (95% CI, 1.40 to 5.61%) of patients infected with *Campylobacter*, mainly with *C. jejuni* and *C. coli*, developed reactive arthritis (186), suggesting that the incidence rate of *Campylobacter*-associated reactive arthritis is largely dependent on the geographic regions and cohorts used.

Complications of the Reproductive System

C. jejuni, *C. coli*, *C. fetus* subsp. *fetus*, and *C. upsaliensis* have been shown to cause septic abortion and neonatal sepsis in humans and animals (259, 260). These species are generally associated with abortion in pregnant women following an aggressive bowel infection that results in sepsis, with the infection eventually transmitted to the fetus (259). The clinical presentation and outcome of abortion caused by *Campylobacter* do not differ between species.

Other *Campylobacter* species, such as *C. rectus* and *C. curvus*, have been associated with premature birth and low birth weight in pregnant humans or mice (146, 261, 262). It has been shown that *C. rectus* translocates from the oral cavity to the reproductive tract, leading to inflammation that results in preterm birth (146). In mice, this inflammation appears to be mediated by the activation of Toll-like receptor 4 (TLR4) in placental tissues infected with *C. rectus* (262, 263). It remains to be seen if similar mechanisms control the inflammation that leads to preterm birth and intrauterine growth restriction following *Campylobacter* infection in humans.

CLINICAL MICROBIOLOGY

Isolation Methodologies in Clinical Settings

There is no gold standard or common method for the isolation of all *Campylobacter* species from clinical samples. Several selective agar media, using blood-based agar or blood-free agar, have been used for the isolation of *Campylobacter* species, particularly thermotolerant species (2). However, given the variability in antibiotic susceptibilities among *Campylobacter* species, these methods are effective for only a subset of species.

A more robust method—the Cape Town protocol—requires filtration of homogenized clinical samples through membrane filters with a pore size of 0.45 or 0.65 μm onto blood agar media (with or without vancomycin supplementation). The plates are then incubated at 37°C under microaerobic conditions (~5% O_2) enriched with CO_2 and H_2 (264). While not an absolute requirement, H_2 enhances the growth of some *Campylobacter* species. The Cape Town protocol has been used successfully to isolate a range of *Campylobacter* species from fecal, intestinal biopsy, and saliva samples (264).

Enrichment procedures have been suggested to improve isolation rates from samples with a small starting number of *Campylobacter* cells (e.g., intestinal biopsy specimens). Enrichment of homogenized intestinal biopsy specimens in Ham's F-12 medium supplemented with vancomycin, followed by incubation at 37°C for 2 days and in combination with the Cape Town protocol, has been effective for the isolation of a number of *Campylobacter* species from patients with chronic gastroenteritis and IBD (108). Other enrichment broths that have been used to successfully isolate *Campylobacter* species include brucella-FBP (a combination of ferrous sulfate, sodium metabisulfite, and sodium pyruvate), Preston, Doyle and Roman, modified charcoal cefoperazone deoxycholate, Park and Sanders, Bolton, Hunt and Radle, and Hunt broths (265).

Laboratory Diagnosis

Laboratory diagnosis of *Campylobacter* infection requires the use of culture-dependent and/or culture-independent methodologies. In culture-dependent methodologies, single isolated colonies can be subjected to a range of conventional biochemical tests to identify phenotypic traits. Temperature, incubation time, and atmospheric conditions, for example, an H_2-enriched atmosphere or growth at 42°C, can also be used to favor the growth of *Campylobacter* species during isolation procedures. The biochemical profile of an unknown organism is then matched to previously defined characteristics of the *Campylobacter* genus/species to enable identification of the organism to the genus or species level. In culture-independent methodologies, DNA or RNA can be isolated from clinical samples or from a pure culture. A genetic signature or marker of the organism can then be determined using sequencing techniques or genus- or species-specific PCR amplification of the gene of interest, for example, the 16S rRNA gene. Culture-independent tests are increasingly being used for the detection of *Campylobacter* species, and while in many cases they can enhance detection sensitivity, it has been proposed that this will have an impact on public health surveillance given that detailed analyses of isolates are required to monitor the distribution of different strains (266).

Biochemical identification. Biochemical tests can be used to differentiate *Campylobacter* species from related genera and to identify organisms to the species level (2). The relevant biochemical tests used to differentiate between members of the *Campylobacter* genus have been reviewed by Lastovica (80). In that article, a biochemical flowchart to identify *Campylobacter* species is outlined, beginning with growth with or without supplementation of H_2, followed by an indoxyl acetate test, a hippurate test, growth on MacConkey agar, an aryl sulfatase test, and production of H_2S. Furthermore, detection of L-alanine aminopeptidase activity can be employed to differentiate between *Campylobacter*, *Helicobacter*, and *Arcobacter* species and other Gram-negative bacteria (80). However, the ability to differentiate between *C. jejuni* and *C. coli* would be the most relevant in the clinical setting. The only biochemical test that distinguishes between these two species is the hippurate hydrolysis test. *C. jejuni* isolates have the ability to hydrolyze hippurate, whereas *C. coli* isolates yield a negative test result.

Molecular identification. The 16S rRNA gene has been used extensively for rapid detection and identification of many bacterial taxa, including *Campylobacter* species (267, 268). Owing to the sequence similarity among *Campylobacter* species, the 16S rRNA gene sequence cannot be used to differentiate between very closely related species, such as *C. jejuni* and *C. coli* (269). The larger 23S rRNA gene and the internal transcribed spacer (ITS) region, a

region which lies between the 16S and 23S rRNA genes, have also been used to differentiate between *Campylobacter* species and strains (270–272). The 23S rRNA genes contain strain-specific intervening sequences, whereas the ITS region is highly variable in size and sequence composition depending on the species (273, 274). Indeed, a comprehensive analysis revealed the ITS region to be the most discriminatory region, compared with the 16S and 23S rRNA genes, for species and strain differentiation for the *Campylobacter* genus (270). When all three regions (16S rRNA-ITS-23S rRNA) were combined to create a phylogenetic tree, the resultant tree had the highest resolution in differentiating between members of the *Campylobacter* genus (270).

Several enzyme immunoassays are also available for the detection of *C. jejuni* and *C. coli* in clinical samples. A recent study by Granato and colleagues compared three commercially available kits with culture-based techniques and found that the three immunoassays had sensitivities that ranged from 98.5 to 99.3% and specificities that ranged from 98.0 to 98.2%, while standard culture had a sensitivity of 94.1% (275). Furthermore, a number of real-time assays are also available for the detection of *Campylobacter* species, some of which are capable of detecting more than one species at a time, including *C. jejuni*, *C. coli*, and *C. lari* (57). Interestingly, Javed and colleagues also described an assay to detect *C. jejuni* and *C. coli* based on the ability of recombinant receptor binding proteins from the *C. jejuni* bacteriophage NCTC12673 to agglutinate in the presence of these species (276).

More recently, due to the reduced costs of bacterial genome sequencing, the genomes of *Campylobacter* species and strains can now be sequenced fully, and many of these are completed or drafted. To date, the complete and draft genomes of over 100 *Campylobacter* species or strains—predominantly *C. jejuni* and *C. coli* strains—are available in the NCBI database. Genome sequencing and assembly have become commonplace in research labs for the characterization of isolates, and this will likely become routine practice in diagnostic facilities in the future.

Antibiotic Therapies

Most *Campylobacter* infections are self-limiting and require no therapeutic intervention other than supportive therapy, such as maintenance of hydration and electrolyte balance. However, antibiotics are employed in immunocompromised patients, patients whose symptoms are severe or persistent, and those with extraintestinal infections (277, 278).

Ciprofloxacin, a fluoroquinolone, is often used for the empirical treatment of gastroenteritis, particularly in travel-related cases. The major targets of quinolones in bacteria are DNA gyrase and topoisomerase IV, which are enzymes essential for DNA replication, transcription, recombination, and repair. However, in the case of campylobacteriosis, macrolides are the preferred choice of therapy (279). Macrolides bind to the 23S rRNA nucleotides 2,058 and 2,059 in the 50S ribosomal subunit, which results in blockage of the translocation step of protein synthesis, thereby preventing release of tRNA after peptide bond formation and resulting in the termination of peptide chain elongation. The reason for the increasing importance of macrolides for the treatment of *Campylobacter* infections is that the rates of ciprofloxacin resistance are relatively high for *Campylobacter* species due to the use of antibiotics in the poultry industry and animal husbandry operations (discussed further below) and, to a lesser extent, the indiscriminate use of ciprofloxacin for treatment of human diseases (280). This is particularly important in developing countries, where the use of fluoroquinolones is usually a suboptimal approach, for the above-mentioned reasons. For example, a recent randomized double-blind trial conducted in Thailand that compared macrolide regimens (single-dose and 3-day azithromycin treatments) with a fluoroquinolone regimen (3-day levofloxacin treatment) for the empirical management of traveler's diarrhea, mainly caused by *C. jejuni*/*C. coli* (64%), reported a cure rate of 96% with azithromycin, compared to 71% with levofloxacin (281). Similarly, the rate of microbiological eradication was superior with azithromycin-based regimens (96% to 100%) compared to the levofloxacin regimen (38%) ($P = 0.001$) (281). The high efficacy of azithromycin was supported by a further study comparing a single-dose azithromycin regimen to a 5-day erythromycin treatment in children with campylobacteriosis, which showed that azithromycin was significantly superior to erythromycin in eradicating the pathogen and accelerating the time to clinical cure (282).

A number of macrolides are also used in food animal production for both growth promotion and therapeutic reasons (283), and this has resulted in high levels of macrolide resistance being reported in some countries (284, 285). Consequently, ciprofloxacin has been recommended for the treatment of human infections caused by macrolide-resistant *Campylobacter* species.

Another problem related to antibiotic resistance in *Campylobacter* infections is the emergence of multidrug-resistant (MDR) strains (defined as strains with resistance to three or more antibiotics), which have been isolated in many countries throughout the world. The levels of MDR strains in humans are still relatively low overall (<25%) (286), but an increase in these strains in domesticated animals has raised concerns in relation to human disease (287). These concerns are well placed given that infections with *Campylobacter* species which are resistant to antibiotics have been associated with a longer duration of illness, an increased risk of invasive disease and death, and increased health care costs (288–290). In the case of severe *Campylobacter* infection in humans, treatment with aminoglycosides (e.g., gentamicin or kanamycin) is commonly employed (291). The mechanism of action of aminoglycosides involves binding to the 30S ribosomal subunit, where they interfere with the binding of formylmethionyl-tRNA to the ribosome, preventing the formation of the initiation complexes from which protein synthesis proceeds, and the rate of resistance to these antibiotics remains relatively low for *Campylobacter* species (3%) (286, 292).

RISK FACTORS, TRANSMISSION, AND ENVIRONMENTAL RESERVOIRS

A number of risk factors contribute to the susceptibility of humans to campylobacteriosis. A recent meta-analysis revealed that international travel was the most important risk factor for campylobacteriosis (OR, 4.9; 95% CI, 2.9 to 8.2), followed by consumption of undercooked chicken, environmental exposure, and direct contact with farm animals (293). In agreement with this, another study revealed that international travel was a risk factor for infection, with *C. jejuni* being one of six organisms that contributed to 70% of all gastrointestinal infections acquired during overseas travel between 1996 and 2005 (294). Moreover, campylobacteriosis was found to be the main cause of travel-related disease in Canada from 2005 to 2009, being responsible for 27.6% (123/446 cases) of cases (295). Similar levels have been reported in

the United States, with 18% of *Campylobacter* infections being estimated to be associated with international travel (296). Domestic travel also plays a role in the transmission of human campylobacteriosis (297). In Europe, the proportion of diarrhea cases caused by *Campylobacter* species detected in travelers increased from 7% in 2008 to 12% in 2010 (298). In England, 17% of *Campylobacter* infections were classified as being associated with travel (299).

The level of risk for travel-related campylobacteriosis appears to be associated with the travel destination. A meta-analysis in 2009 showed that the locations with the highest levels of risk are Southeast Asia (32.4%; 162/500 cases), South Asia (7.8%; 39/499 cases), Africa (4.6%; 54/1,177 cases), and Latin America (2.5%; 51/2,031 cases) (300). More recently, Mughini-Gras and colleagues found that Dutch travelers visiting South Asia (OR, 28.9; 95% CI, 2.4 to 265.1), Southeast Asia and China (OR, 27.8; 95% CI, 4.5 to 170.9), sub-Saharan Africa (OR, 25.4; 95% CI, 2.7 to 310.7), Latin America and the Caribbean (OR, 20.8; 95% CI, 2.0 to 211.6), western Asia (OR, 10.6; 95% CI, 2.8 to 39.9), and northern Africa (OR, 10.6; 95% CI, 2.3 to 49.0) were at higher risk of developing campylobacteriosis than those traveling to western European countries. While travel does contribute to the overall burden of *Campylobacter* transmission, the transfer or spread of exotic or antibiotic-resistant strains to previously unexposed populations is a further concern. In addition, travel-related infections are often associated with consumption of contaminated meat or water (300), suggesting that a complex interrelationship exists between risk factors.

Consumption of contaminated food, particularly poultry products, unpasteurized milk, and water, is a risk factor for *C. jejuni* and *C. coli* infection (Fig. 1) (18, 301, 302). One approach to estimate the source attribution of campylobacteriosis cases is through the analysis of outbreak data. As expected, *Campylobacter* infections are mainly attributed to poultry products by using these techniques (303, 304). More recently, however, molecular techniques, such as multilocus sequence typing, *porA*/*flaA* typing, and gyrase subunit A typing, have played a more significant role in source attribution (305–310), allowing further insights into the contributions of the different reservoirs to the burden of campylobacteriosis in humans and the subsequent transfer of *Campylobacter* species to wildlife through environmental contamination.

Immunodeficiency is also a risk factor for campylobacteriosis (101, 311). For example, human immunodeficiency virus (HIV)-infected patients presenting with diarrhea are more frequently infected with *Campylobacter* than uninfected individuals with diarrhea (311). In addition, the incidence of *Campylobacter*-related illness among HIV-infected patients is higher than the incidence found in the general population (312). Below, we further examine the prevalence of *Campylobacter* species in the environment and discuss how these reservoirs facilitate transmission of *Campylobacter* to humans.

Poultry

Poultry is recognized as a primary source of food-related transmission of *Campylobacter* species to humans (313). A major contributing factor is the high carriage rate of *Campylobacter* within broiler chickens. Therefore, *Campylobacter* species are found in abundance on poultry farms and their surrounding environment, including the soil, water sources, dust, building surfaces, and the air (314). In addition to chickens, commercial turkeys and ducks can also serve as reservoirs of *C. jejuni* and *C. coli* (315–317). Furthermore, poultry is also an important reservoir of other *Campylobacter* species, such as *C. lari*, *C. upsaliensis*, and *C. concisus* (318, 319). Domesticated broiler chickens and imported chickens both contribute to the overall burden of *Campylobacter* infections (320).

It has been estimated that 71% of human campylobacteriosis cases in Switzerland between 2001 and 2012 were attributed to chickens (321, 322). A study investigating the prevalence of *Campylobacter* in crop (enlarged part of the digestive tract of birds that serves as a temporary storage space for food) and cecal samples from market-age broiler chickens found 62% of crop samples to be positive, compared to only 4% of cecal samples ($P < 0.001$), suggesting that the crop is an important niche for *Campylobacter* and may represent a major source of contamination during processing (323). Given that *C. jejuni* strains survive in chicken feces for up to 6 days after excretion, chicken feces may also be a potential source of transmission to the environment or humans when poultry manure is used as a fertilizer (324).

The UK Food Standards Agency reported preliminary findings showing that 72.9% of fresh whole retail chickens surveyed during 2014 to 2015 were infected with *Campylobacter*, with 18.9% of these harboring a level of >10,000 CFU/g, which is considered highly contaminated (325). Data from Canada also support the finding that broiler chickens are a major source of *Campylobacter* species. There are, however, indications that chicken-associated *Campylobacter* infections may be more common in urban dwellers than in rural dwellers (326, 327). One study reported the levels of thermotolerant *Campylobacter* species to be three times higher in organic broilers than in conventional broilers (54.2% versus 19.7%) (328), suggesting that the likelihood of purchasing *Campylobacter*-contaminated broiler meat is higher for organic sources than for conventional sources. Furthermore, the relative risk of becoming ill from *Campylobacter* on a per-serving basis is 1.7 times higher for consuming organic carcasses than for consuming conventional carcasses.

Domesticated Animals

Domesticated animals are another reservoir of *Campylobacter* species (313, 329). Fresh and frozen meats are frequently contaminated with *Campylobacter*, whereas commercial cooked products are less affected (1, 330). *C. jejuni*, *C. coli*, and *C. lari* accounted for 69, 30, and 1% of the contaminating bacteria in these products, respectively (330). In addition to consumption of contaminated meat from domesticated animals, contact with domesticated and companion animals poses a significant risk for the transmission of *Campylobacter* species (1, 301, 302, 321, 331, 332).

Recent studies from Denmark showed that cattle were the attributed source for 16 to 17% of the total cases of campylobacteriosis (320). Similarly, in Switzerland, cattle have been estimated to be responsible for 19.3% of *Campylobacter* infections, which is substantially higher than the contribution from pigs (1.2%) (321). The prevalence of *Campylobacter* in cattle varies significantly across studies, with rates ranging from 23% to close to 90% (333–335). The species detected in cattle include *C. jejuni*, *C. coli*, *C. lari*, and *C. lanienae* (335–337).

Campylobacter species are also prevalent in pigs and piglets. These bacteria are capable of colonizing piglets as early as 24 h after birth, as a result of exposure to contaminated feces (338). The carriage rates of *Campylobacter* range from 32.8 to 85.0%, de-

pending on the age of the pig (339, 340). Similar to the trend in cattle, younger pigs tend to have higher levels of *Campylobacter* than older animals (333, 339). However, in contrast to cattle, pigs are more readily colonized by *C. coli* (340).

Sheep and goats have also been investigated for their rates of carriage of *Campylobacter* species. In Nigeria, 6.8% of intestinal samples from sheep were found to be positive for *C. jejuni*, *C. coli*, or *C. lari* (341). A higher prevalence rate (17.5%) was reported for cecal samples from sheep from Swiss abattoirs, with only *C. jejuni* and *C. coli* being detected (342). In both studies, *C. jejuni* was the major *Campylobacter* species detected (341, 342). Screening of fecal samples from 222 dairy goats on 12 farms in Spain failed to detect any *Campylobacter* species (343).

Dogs and cats are also carriers of *Campylobacter* species (344). Up to 58% of healthy dogs and 97% of diarrheic dogs have been determined to be positive for *Campylobacter* species (345). Interestingly, *C. upsaliensis* appears to be one of the major *Campylobacter* species colonizing dogs and cats (344); however, *C. coli*, *C. concisus*, *C. fetus*, *C. gracilis*, *C. helveticus*, *C. jejuni*, *C. lari*, *C. mucosalis*, *C. showae*, and *C. sputorum* have all been detected in these animals (345). Other domesticated animals that have been investigated as potential reservoirs of *Campylobacter* species include hamsters (346, 347), ferrets (348), pet reptiles (349), and rabbits (350). Based on the low rates of carriage of *Campylobacter* species in these animals, it is probable that they are not a major source of transmission of *Campylobacter* species to humans.

Wild Animals

Wild animals are potential reservoirs of *Campylobacter* species. Among all the host species studied, wild birds are most likely to carry *Campylobacter* species. Indeed, 35% of the cecal contents harvested from 445 wild ducks from Colorado tested positive for *C. jejuni* (351). A study in Norway examined 540 wild birds of 40 different species and found that 28.4% were positive for *C. jejuni*; crows, puffins, and gulls had the highest carriage rates, i.e., 89.8%, 51.3%, and 50.0%, respectively (352). A similar carriage rate was observed in wild birds in Italy (74/217 birds; 34.1%) (353).

Studies of other types of wild birds have reported lower *Campylobacter* carriage rates. For example, Llarena and colleagues examined fecal samples from 924 barnacle geese and reported the prevalences of *C. jejuni* to be 11.5% and 23.1% in 2011 and 2012, respectively (354). In the same study, the prevalence of *C. coli* in both 2011 and 2012 was only 0.2%. Furthermore, a study conducted in Norway failed to detect *C. jejuni* in geese. In contrast, 3.0% (6/200 birds) of pigeons and 20.0% (1/5 birds) of mallards carried *C. jejuni* (355). The prevalence of *C. jejuni* in waterfowl in northeastern Spain (318 adult waterfowl of nine fowl species) was 12.6% (356). A further study in Spain isolated *C. jejuni* from 1.0% (1/97 birds) of griffon vultures (357), while a study from the United States, conducted over the period from 2009 to 2010, isolated thermophilic *Campylobacter* species from 4.8% (9/188 birds) of captured wild birds (358). These results indicate that the prevalence of *Campylobacter* species varies greatly depending on the type of wild birds and their geographic regions.

Other wild animals tested for the presence of *Campylobacter* species include small rodents, deer, moose, reindeer, boars, mangabeys, porcupines, duikers, and turtles—all were found to have low levels or to be free of *Campylobacter* species (355, 358–362). Furthermore, a number of studies have suggested that the importance of wild animals as a reservoir of infection is limited, as strains isolated from wild animals are usually not clonally related to isolates from humans and chickens (317, 363, 364). This is in contrast to a number of studies which reported that *Campylobacter* strains isolated from wild bird feces around broiler houses can be recovered from the ceca of broilers in those houses (365–367). These studies provide evidence for the contribution of wild birds to *Campylobacter* contamination during poultry production and processing and suggest a potential role in human campylobacteriosis. Overall, current studies indicate that only some species of wild birds have high rates of carriage of *Campylobacter* species and that, currently, insufficient evidence exists to determine whether these isolates play an important role in human disease.

Water

Water is an effective vehicle of transmission of *Campylobacter* species to humans and animals, and contaminated water has been responsible for a number of outbreaks in different countries (368–371). Drinking undisinfected water is a leading risk factor for campylobacteriosis (372). Several studies have assessed the prevalence of *Campylobacter* species in different water sources. For example, Arvanitidou and colleagues isolated *C. jejuni* from 1.0% of drinking water samples (5/500 samples) in northern Greece (373). In Poland, Popowski and colleagues detected *C. jejuni*, *C. coli*, or *C. lari* in 70% of water samples from rivers or lakes in the Warsaw region (374), supporting a role for contaminated water in the direct transmission of *Campylobacter* species to humans. Individuals who utilize private wells rather than municipal surface water systems as a drinking water source are at a higher risk of developing campylobacteriosis than other reportable enteric diseases (375).

Farms that utilize private water supplies as a water source for their cattle are more likely to have cattle that test positive for *Campylobacter*, indicating that contaminated water can also serve as a means of transmission of *Campylobacter* to domesticated animals (334). Indeed, emptying and cleaning water troughs more regularly have been shown to reduce the risk of colonization of cattle by *Campylobacter* (334). Furthermore, it has been reported that cattle were more likely to test positive for *Campylobacter* following an outdoor grazing period in spring, when the water supply was lake water, than when they were confined indoors in winter, when their water supply was municipal chlorinated tap water (376). Other sources implicated in the contamination of outdoor water are wild bird feces and waste runoff from contaminated domesticated animals (377).

Given that contaminated water may be a common factor in transmission to different hosts, its role in the transmission cycle and as a source of *Campylobacter* contamination or infection may be underestimated. Indeed, Champion and colleagues showed that *C. jejuni* isolates from different sources (humans, chickens, bovines, ovines, and the environment) cluster into two clades: a "livestock clade" and a "nonlivestock clade." Of these, 55.7% of human and 11.4% of livestock isolates were reported to group within the nonlivestock clade (378), suggesting that the environment, and particularly water sources, may be an underestimated reservoir for transmission of *Campylobacter* species.

Other Sources

Although it is not as common, another potential source of transmission is person-to-person transmission (fecal-oral or via fomites). The Health Protection Agency in the United Kingdom

found that person-to-person transmission was the source of outbreaks in 3% (5/143 cases) of the campylobacteriosis cases from 1992 to 2009 (31). Furthermore, a study conducted in New Zealand that combined detailed epidemiological and genotyping data concluded that person-to-person transmission was responsible for 4% of campylobacteriosis cases in that country (74). Other studies, conducted in Australia and the Netherlands, provided similar figures for the contribution of person-to-person transmission to campylobacteriosis (300, 379).

Unpasteurized milk sourced from dairy cattle has also been implicated in a number of campylobacteriosis outbreaks (380–382). The number of outbreaks in the United States associated with unpasteurized milk increased from 30 in 2007 to 2009 to 51 in 2010 to 2012 (383). Unpasteurized milk may also serve as a source of several other *Campylobacter* species, including *C. hyointestinalis* subsp. *hyointestinalis*, *C. fetus* subsp. *fetus*, *C. concisus*, and *C. ureolyticus* (384, 385). Genomic analyses indicate that the presence of *Campylobacter* species in milk can be attributed to fecal contamination (386).

Several other transmission sources, including insects, have been investigated as reservoirs of *Campylobacter* species. For example, flies have been suggested to play a role in the transmission of *Campylobacter* species from contaminated sources to broiler chickens (387), and the lesser mealworm beetle, *Alphitobius diaperinus*, may act as a reservoir of *C. jejuni* (388). In one study, *C. jejuni* was reported to survive on the exterior of the beetle for 12 h and in the interior of larvae for 72 h, and it could be shed in the feces of larvae for 12 h after exposure. In this study, 90% of birds that consumed a single adult or larval beetle became *C. jejuni* positive, while 100% of those that consumed 10 adults or larvae became positive, a finding that suggests that beetles are capable of passing viable bacteria to chickens (388). In contrast, Skov and colleagues found that litter beetles, which are commonly present in chicken houses, do not play an important role as reservoirs of *Campylobacter* species (389). It is possible that only specific species of beetles are carriers of *Campylobacter* species.

Studies have also suggested that microbial eukaryotes may act as a nonvertebrate reservoir of *Campylobacter* species in the environment. For example, in a study by Axelsson-Olsson and colleagues, *C. jejuni* was found to survive longer when it was cocultured with the protozoan *Acanthamoeba polyphaga* than when it was cultured alone (390). Microscopically, *C. jejuni* was found to aggregate in vacuoles within amoebae, and it could be detected following rupture of the eukaryotic cells (390). Since a diverse range of microbial eukaryotic organisms (73.5% yeasts and fungi and 26.5% protozoa) are found in the poultry drinking water systems on farms (391), it is not surprising that eukaryotes infected with *Campylobacter* may play a role in the transmission of this organism to chickens.

IMPACT OF ANTIBIOTIC USAGE IN ANIMALS ON *CAMPYLOBACTER* RESISTANCE

The discovery in 1950 that the addition of antibiotics to animal feed at subtherapeutic levels could lead to increased growth rates in husbandry animals resulted in research into methods to improve or stabilize meat supplies to the consumer. Indeed, by the turn of the 20th century, the majority of antibiotic usage in the United States was for agricultural purposes. This approach has led to a dramatic increase in antibiotic resistance in several human pathogens that originate from domesticated animals, including *Campylobacter* species (392).

As early as 1999, Smith and colleagues reported an increase in quinolone-resistant *C. jejuni* in Minnesota residents, whose acquisition could be attributed to foreign travel and poultry products (393). Smith et al. proposed that the use of fluoroquinolones in the poultry industry, which started in the United States in 1995, was in part responsible for the increase in prevalence of quinolone-resistant *C. jejuni* (from 1.3% in 1992 to 10.2% in 1998; $P < 0.001$) (393). There is strong evidence to support the observation that fluoroquinolone use in food animals is associated with increased numbers of infections with resistant strains of *Campylobacter* in humans. Indeed, therapeutic fluoroquinolone administration to poultry flocks has been shown to select for ciprofloxacin-resistant *C. jejuni* in poultry (394). However, an increase in antibiotic resistance in *Campylobacter* isolates from poultry is not restricted to *C. jejuni*. In 2013, Wieczorek and colleagues found that *C. coli* had higher levels of resistance than *C. jejuni*, irrespective of the antimicrobial agents tested, including ciprofloxacin, nalidixic acid, tetracycline, and streptomycin (395).

This increase in antibiotic resistance has also been observed in *Campylobacter* isolates from cattle. For example, in a study by Di Labio and colleagues, investigation of antimicrobial resistance in 202 *Campylobacter* isolates from Swiss veal calves showed 67.8% of isolates to be resistant to at least one of the agents tested (396). Importantly, resistance mainly corresponded to antimicrobial agents that were utilized in the farming processes. In France, a 5-year survey of fecal samples from cattle between 2002 and 2006 recovered *Campylobacter* species from 16.5% of 2,255 samples (*C. jejuni* from 12.8% and *C. coli* from 3.7%). Investigation of the antibiotic susceptibility of these *Campylobacter* species showed an increase in the rates of resistance to quinolones and fluoroquinolones from 2002 to 2006, with the fluoroquinolone resistance rate rising from 29.7 to 70.4% (397). Interestingly, fluoroquinolones are not utilized in Australian livestock, and as a result, *Campylobacter* isolates from livestock in this region have negligible levels of resistance to fluoroquinolones, which in turn correspond to low resistance levels in human isolates (398). Low levels of resistance to quinolones are also observed in Finland and Sweden (284).

Similar to the case for cattle and poultry, the rate of macrolide resistance has been found to be high in *C. coli* isolates from pigs in Switzerland, a finding that reflects the use of these antimicrobials in Swiss livestock production (399). Indeed, the use of tylosin, erythromycin, and tilmicosin in pigs is considered a major driving factor of resistance to macrolides (400). While antibiotic use in agriculture is still commonplace in many countries, a number of countries have implemented bans on the nonmedicinal use of antimicrobials in livestock. It remains to be seen if such bans will result in a decrease in resistance rates in these countries.

CONTROLLING THE SPREAD OF CAMPYLOBACTERIOSIS

Current estimates suggest that transmission of 50 to 80% of all human cases of campylobacteriosis is related to chickens (401). The annual worldwide costs associated with *Campylobacter* infection are extremely high. For example, in the United States, the estimated annual cost of campylobacteriosis is reported to be $1.3 billion, while in the Netherlands, it is estimated to be €21 million (32, 52). Given the association between chickens and campylobacteriosis, as well as the high costs associated with this disease, many countries have invested in developing strategies to control the

dissemination of *Campylobacter* species in the poultry industry (27). These strategies target a number of key areas, including reducing environmental exposure, reducing or removing *Campylobacter* from colonized chickens, and increasing the resistance of chickens to *Campylobacter* carriage. Based on an appraisal of all the literature published between 1980 and September 2008, Newell and colleagues have written an excellent review on *Campylobacter* and biosecurity on poultry farms, which outlines the different routes of transmission that occur on poultry farms and the degrees of success of strategies undertaken to prevent transmission of *Campylobacter* (402). We further highlight below the various methodologies that have been used to control *Campylobacter* transmission.

Reducing *Campylobacter* Transmission in Chickens

Horizontal transmission of *Campylobacter* in the farm environment represents the usual route of transmission. Once *Campylobacter* is introduced into a chicken flock, it spreads rapidly and results in colonization of the intestinal tracts of the majority of chickens within 1 week. The primary sites of colonization within the intestine are the crop, ceca, and small intestine (402, 403). In contrast, vertical transmission of *Campylobacter* from an infected bird to its offspring via internal contamination of eggs within the reproductive tract prior to shell formation is rare, although "pseudo-vertical transmission" of microorganisms from parent flocks to their chicks via fecal contamination of shells can occur (402). Once colonized, chickens remain colonized until they are slaughtered. Although they are colonized by large numbers of *Campylobacter* organisms (up to 10^9 bacteria/g), chickens usually exhibit no clinical or other adverse effects (402). An interesting study, however, recently showed that *C. jejuni* infection of some chicken breeds can lead to prolonged inflammation, damage of the gut, and diarrhea (404).

Human and vehicular traffic entering farms also appears to be an important route for *Campylobacter* species to enter poultry houses from the external environment. In particular, staff who handle neighboring livestock, especially poultry, are associated with an increased risk of *Campylobacter*-positive flocks, and the number of staff employed to look after the house and the frequency of visits per day are also associated with the level of risk (402). Given the abundant source of *Campylobacter* species on poultry farms and their environment, strict hygiene measures have been introduced on the majority of farms in an attempt to reduce *Campylobacter* colonization of chicks, although adherence to these measures differs considerably from farm to farm. Based on the current literature, the use of hygiene barriers at the entrance to poultry houses, the provision of hand-washing facilities, the performance of boot dips, and the use of house-specific boots and overshoes have all been shown to significantly decrease *Campylobacter* colonization of chicks (314, 402).

Although study results are conflicting, it appears that in some countries flies play an important role in transmitting *Campylobacter* species from fecal sources to poultry (402). For example, in a recent study conducted in Denmark, the prevalence of *Campylobacter*-positive flocks was reported to have reduced significantly, from 41.4% in 2003 to 2005, before fly screens were introduced, to 10.3% in 2006 to 2009, after fly screens were installed ($P < 0.001$; OR, 6.1; 95% CI, 3.1 to 12.4) (405). Furthermore, that study showed that over the summer period, no rise in the prevalence of *Campylobacter* species was observed in poultry houses with fly screens, while over the same period poultry houses without fly screens showed significant increases. Based on their findings, the authors estimated that if fly screens had been part of Danish biosecurity practices, the prevalence of *Campylobacter*-positive flocks during summer months could have been reduced by approximately 77% nationally (405).

Another important source of *Campylobacter* on chicken farms is fecal material from chickens already colonized with *Campylobacter* living on the same farm; the risk of colonization in a flock is associated with the presence of older birds (402). The number of chicken houses on the farm also appears to be an important factor, although the relationship between the number of houses and the level of increased risk appears to differ by geographic location. For example, in France, an increased infection risk was associated with three or more houses on the same site, while in the Netherlands, having five or more houses has been reported to give an elevated risk (402). Based on the finding that identical *Campylobacter flaA* types were present in isolates obtained from birds originating from different hatcheries, it has been suggested that flocks are colonized by *C. jejuni* following placement of chicks into broiler chicken houses and that *C. jejuni* strains within the farm are those carried over from the previous flock (406). Reductions in intestinal colonization levels of broiler chickens have been reported to lead to a considerable decline in the incidence of campylobacteriosis (407). Indeed, Rosenquist and colleagues reported that a 2-$\log_{10}$ reduction of *Campylobacter* levels on broiler carcasses resulted in a 30-fold decline in the incidence of human campylobacteriosis (328). Given this, a number of strategies aimed at reducing *Campylobacter* colonization in poultry, including the use of bacteriocins, bacteriophages, and probiotics, have been investigated.

Bacteriocins. One approach to reduce *Campylobacter* colonization in chickens is the use of bacteriocins. Bacteriocins are antimicrobial peptides produced by a range of bacterial species. A number of effective anti-*Campylobacter* bacteriocins have been identified in commensal bacteria isolated from the intestines of chickens and are currently being investigated for the ability to control *Campylobacter* species at the farm level. For example, in a study by Svetoch and Stern, treatment of chickens with the bacteriocin L-1077, produced by *Lactobacillus salivarius* strain L-1077 isolated from broiler chickens, resulted in decreases in cecal *C. jejuni* counts of >4 log compared with those for untreated control birds (408). In addition, the effects of three other bacteriocins, OR-7 from *Lactobacillus salivarius* and E-760 and E50-52 from *Enterococcus faecium*, have been investigated (409). Administration of these three bacteriocins to chickens resulted in dramatic reductions of 5 to 8 $\log_{10}$ CFU in *C. jejuni* intestinal colonization (409). Investigation of the development of resistance of *Campylobacter* species to the E-760 bacteriocin *in vitro* indicated that low-level but not high-level bacteriocin resistance can be developed. Furthermore, in a chicken model of *Campylobacter*, the E-760 bacteriocin again selected only for low-level bacteriocin-resistant *C. jejuni* mutants. In the absence of bacteriocin selection pressure, this low level of bacteriocin resistance was shown not to be stable either *in vitro* or *in vivo*. Collectively, these findings indicate that bacteriocins may be promising agents for the control of *C. jejuni* in commercial broiler chickens.

Bacteriophages. Bacteriophages have also been investigated for use in the biocontrol of *Campylobacter* species. The use of bacteriophages to reduce *Campylobacter* cecal colonization of chickens has shown encouraging results as far as reducing *Campylobacter*

counts. A number of studies have reported that under experimental conditions, bacteriophage treatment of chickens which have already been colonized with *Campylobacter* results in reductions of 0.5 to 5.0 $\log_{10}$ CFU/g *Campylobacter* in the chicken gut (410–414). For example, in a field trial by Kittler and colleagues, a phage cocktail at levels of 5.8 to 7.5 $\log_{10}$ PFU/bird was added to the drinking water of chickens colonized with *Campylobacter*, and the results showed that, at slaughter, *Campylobacter* counts in the ceca of treated birds were significantly reduced (>3.2 $\log_{10}$ CFU/g cecal content) compared with those of the control group ($P = 0.0011$) (415).

While these results are encouraging, *Campylobacter* numbers generally return to pretreatment levels over time (416). One explanation for the lack of longevity in the reduction of *Campylobacter* numbers is the development of resistance to phage therapy (416). Given this, it has been suggested that bacteriophage treatment immediately prior to slaughter might be a better approach, as this has the potential to reduce the cecal *Campylobacter* load and, as a result, reduce infection in humans (416). Evidence exists to show that the rate of resistance to phage therapy can be reduced by administering multiple phages at the same time. For example, in a study by Fischer and colleagues, commercial broilers were inoculated with 10^4 CFU of a *C. jejuni* field strain (417), after which three groups of birds ($n = 88$ per group) were treated with either a single phage, a four-phage cocktail, or solvent only. The results showed that following treatment with the single phage and the phage cocktail, *Campylobacter* levels were permanently reduced, with a significant reduction being observed between 1 and 4 weeks posttreatment and a maximum reduction level of 2.8 $\log_{10}$ CFU/g cecal content. Investigation of bacteriophage resistance showed initial resistance rates of up to 43% in those treated with the single phage, whereas a resistance rate of 24% was observed in birds that had received the cocktail. These resistance levels, however, later stabilized at low levels (417). The feasibility of introducing phage therapy as part of poultry farming practices and the costs associated with this process on a large scale are not known.

Probiotics. Probiotics have been shown in some studies to be valuable for inhibiting *C. jejuni* colonization. For example, a study by Ghareeb and colleagues demonstrated that *Enterococcus faecium*, *L. salivarius*, *Lactobacillus reuteri*, and *Pediococcus acidilactici*, originally isolated from the intestines of healthy chickens, could inhibit the growth of *C. jejuni in vitro* (418). In their study, they infected 1-day-old broiler chicks with 10^4 CFU of a field strain of *C. jejuni* orally. The chickens were then randomized into two groups, one of which received a multispecies probiotic (2 mg/chick/day) in their drinking water, while the other group received no probiotic treatment. At both 8 and 15 days postchallenge, cecal colonization by *C. jejuni* was shown to be reduced significantly in chickens treated with probiotics (mean, 3.0 log CFU/g and 2.5 log CFU/g, respectively; $P < 0.001$) compared with controls (mean, 6.8 log CFU/g and 8.0 log CFU/g, respectively; $P < 0.001$) (418). In a similar study by Nishiyama and colleagues, the ability of the probiotic strain *Lactobacillus gasseri* SBT2005 (LG2055) to reduce colonization in chicks was investigated (419). Approximately 24 h following hatching, chickens were infected with *C. jejuni* 81-176, and after 24 h, one group of chickens received LG2005 daily for 14 days, while a second group received no probiotic. At 14 days postinoculation, significantly increased levels of *Lactobacillus gasseri* were observed in chicks receiving *C. jejuni* plus LG2005 compared to those receiving *C. jejuni* alone ($P < 0.001$). Furthermore, a significant reduction in *C. jejuni* levels was observed in the ceca of chicks treated with LG2055 compared with the untreated controls ($P < 0.001$). Santini and colleagues also reported *Bifidobacterium longum* PCB 133 to have a marked anti-*Campylobacter* activity *in vivo* (420). In their study, they initially screened 55 lactic acid bacteria and bifidobacteria *in vivo* for probiotic properties against three strains of *C. jejuni*, with the ultimate goal of finding probiotics that could be used against *Campylobacter* in poultry. Based on their high activity against *C. jejuni* and their ability to survive in the gastrointestinal tract, *Lactobacillus plantarum* PCS 20 and *B. longum* PCB 133 were used in an *in vivo* trial in poultry. While *L. plantarum* PCS 20 showed no effect, *B. longum* PCB 133 gave encouraging results. Following 2 weeks of daily administration of *B. longum* to the chicks, the level of *B. longum* PCB 133 in chicken feces was found to have increased significantly, and it remained high even after a wash-out period of 6 days. Importantly, over the same time frame, the level of *C. jejuni* in chicken feces from chicks administered *B. longum* PCB 133 significantly decreased, showing a 1-log reduction ($P < 0.05$) compared to the level in chicks not receiving the probiotic (420).

Vaccination. Clearly, if it were possible to successfully vaccinate chickens against *Campylobacter*, it would not only reduce *Campylobacter* levels in chickens but also reduce transmission to humans and eliminate postharvest procedures (421). While studies have investigated a range of vaccine candidates over the last 15 years, including the use of flagellar proteins, formalin-inactivated *C. jejuni*, *C. jejuni* inner membrane antigen, and killed *C. jejuni*, delivered intranasally, orally, orally using a *Salmonella* carrier, and intraperitoneally, respectively, none of these vaccines have completely prevented *Campylobacter* colonization in chickens (422). Interestingly, a recent study by Annamalai and colleagues which investigated the effect of nanoparticle-encapsulated outer membrane proteins (OMP) of *C. jejuni* as a vaccine in chickens has shown significant promise (422). In birds that received subcutaneous vaccination, *C. jejuni* colonization levels in cecal and cloacal contents at 7 days postchallenge were shown to be below the detection limit, whereas the other groups showed various degrees of colonization. Based on their study, Annamalai and colleagues considered the subcutaneous route of vaccination, using encapsulated OMP or OMP alone, to be efficacious in eliciting protective antibody responses and preventing colonization of *C. jejuni* in chickens (422).

Strategies aimed at the processing level. *Campylobacter* in the intestinal tracts of chickens at slaughter has the potential to contaminate the slaughterhouse and the food processing environment as well as food products bought by consumers. At the processing level, treatment with organic acids, acidified sodium chlorite, trisodium phosphate, or UV light during primary processing, including the use of chemical dip tanks for carcasses, would help to reduce the number of *Campylobacter* organisms (423). Freezing or irradiating the entire poultry supply would further reduce bacterial numbers by directly killing the pathogen (423). While the postharvest measures outlined above have had some success in reducing the transmission of *C. jejuni* to humans, they do not completely eliminate transmission of *Campylobacter*-related gastroenteritis. In addition, postharvest strategies are expensive and have been reported to degrade the quality of meat (421). Nevertheless, Lake and colleagues have proposed that using multiple interventions at the level of primary processing is the most cost-effective approach to reducing poultry-related transmission, while the use of an irradiation method alone during primary processing is the least cost-effective (423).

Information describing safe food-handling procedures and risk factors associated with campylobacteriosis could be provided to consumers (423). This may help in limiting the level of cross-contamination in the kitchen that results from exposure to contaminated meat. A particular highlight is the success observed in New Zealand following regulatory interventions implemented by the New Zealand Food Safety Authority to reduce *Campylobacter* transmission in the poultry sector. Following the advent of these interventions, the incidence of campylobacteriosis in this country decreased by 50% from 2006 to 2008 (from 383 to 157 cases per 100,000 population) (73). As part of these interventions, poultry processers monitored and reported the prevalence of *Campylobacter* species in poultry flocks and levels of contamination in poultry carcass rinsates, after which mandatory performance targets were introduced. Key improvements were made in regard to hygiene practices in production and primary processing and modifications to the immersion-chiller conditions. In addition, a recent paper found that the prevalence of GBS in New Zealand also decreased as a result of the intervention strategy (184). The successes observed in New Zealand will hopefully encourage other countries which currently do not have regulated interventions in the poultry sector to take action.

CONCLUSIONS

Our evaluation of the epidemiology of campylobacteriosis has revealed an increasingly important role for *Campylobacter* infection in public health. While global efforts to control the transmission of enteric pathogens have been effective at reducing the incidence of a number of major foodborne pathogens, the prevalence of *Campylobacter* infection has nevertheless continued to increase across most developed nations. This rise may be a consequence of many factors, including but not limited to our improved ability to detect these species and our failure to effectively prevent transmission due to breakdowns in biosecurity. There are currently insufficient epidemiological data to provide an accurate assessment of the burdens of campylobacteriosis in Africa, Asia, and Central and South America. However, it is clear that in many of these regions, where data are available, *Campylobacter* species appear to be endemic in children.

The emergence of *Campylobacter* species other than *C. jejuni* and *C. coli* clearly warrants additional investigation. Additional research efforts focusing on their growth conditions, methods of detection, and elucidation of their mechanisms of pathogenesis could revolutionize our understanding of their global distribution and impact on infectious diseases.

It is now well established that poultry, particularly fresh and frozen chicken meat, is a major reservoir of *Campylobacter* species. Other domesticated animals, such as cattle and pigs, and environmental sources, such as contaminated water, also play a vital role in the direct transmission of these organisms to humans. Moreover, many cases of travel-associated *Campylobacter* infection can be attributed to consumption of contaminated meat products or water. Contaminated water contributes to transmission to domesticated birds and other animals, whereas the use of manure from domesticated animals may result in contamination of water sources, fulfilling a cycle of dissemination between natural reservoirs.

The lack of standardized biocontrol methodologies in the poultry sector, a principal source mediating *Campylobacter* transmission to humans, substantially contributes to the global increase in campylobacteriosis. This issue highlights the need for a worldwide campaign to encourage interventions within the poultry sector. The success achieved as a result of an intervention strategy introduced in New Zealand will hopefully inspire other government regulatory bodies to adopt similar methods to combat *Campylobacter* transmission. Without further action, *Campylobacter*-related infection will remain an important infectious disease that challenges global health in the years to come.

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Nadeem O. Kaakoush, Ph.D., undertook his doctoral studies in pathology at the School of Medical Sciences at the University of New South Wales (UNSW), Sydney, Australia, where he investigated pathogenic *Helicobacter* and *Campylobacter* species. Following his doctoral studies, he took up a Research Associate position at the School of Biotechnology and Biomolecular Sciences at UNSW, examining the role of mucosa-associated bacteria in inflammatory bowel diseases. In 2011, Dr. Kaakoush was awarded a National Health and Medical Research Council early career fellowship to further his research in this field, and he has since expanded his research to investigate the overall clinical relevance of emerging *Campylobacter* species.

Natalia Castaño-Rodríguez holds an M.D. from Del Rosario University, Colombia, and an M.Phil. and Ph.D. from the University of New South Wales, Sydney, Australia. She is currently a Research Associate working in the *Helicobacter* and *Campylobacter* laboratory at the University of New South Wales. She has extensive experience conducting research in the fields of microbiology, immunology, and host immunogenetics, with a particular emphasis on the role of pattern recognition receptors in the host inflammatory response following *Helicobacter* and *Campylobacter* infections. More recently, her efforts have been focused on investigation of the role of host immunogenetics in *Helicobacter pylori*-related gastric cancer.

Hazel M. Mitchell was awarded a B.Sc. (with honors) from the University of Strathclyde, Glasgow, United Kingdom, a Dip.Ed. from the Jordanhill College of Education, Glasgow, and a Ph.D. from the University of New South Wales, Sydney, Australia. She previously held the positions of Senior Lecturer and Associate Professor in the School of Biotechnology and Biomolecular Sciences at the University of New South Wales and was promoted to Professor of Medical Microbiology in 2007. Her research studies focus on the role of mucosa-associated bacteria in gastrointestinal disease, in particular the role of emerging *Campylobacter* species and the intestinal microbiota in inflammatory bowel disease and the role of *Helicobacter pylori* and host genetic polymorphisms in gastric cancer. She is on the editorial board of *Helicobacter* and is an Associate Editor of *Gut Pathogens.* She has published 132 peer-reviewed journal articles and 16 book chapters and coedited a book entitled *Helicobacter pylori in the 21st Century*.

Si Ming Man received his B.Med.Sc. (with honors) and M.S. (research) from the University of New South Wales, Sydney, Australia, for his work on *Campylobacter* infection in inflammatory bowel disease. He then obtained his Ph.D. from the University of Cambridge, United Kingdom, where he investigated the role of inflammasome activation in the host defense against *Salmonella* infection. He is a recipient of the National Health and Medical Research Council R. G. Menzies Fellowship and is currently based at St. Jude Children's Research Hospital, Memphis, TN. He has long-standing interests in understanding the molecular mechanisms regulating innate immunity in response to gastrointestinal pathogens. His current research program focuses on elucidating the molecular mechanisms involved in innate immune recognition of bacterial pathogens.