Campylobacter: Animal Reservoirs, Human Infections, and Options for Control

Jaap A. Wagenaar, Diane G. Newell, Ruwani S. Kalupahana, and Lapo Mughini-Gras

Contents

J. A. Wagenaar (✉)
Division of Infectious Diseases and Immunology, Department of Biomolecular Health Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

Wageningen Bioveterinary Research, Lelystad, The Netherlands

WHO Collaborating Center for Reference and Research on Campylobacter and Antimicrobial Resistance from a One Health Perspective/WOAH Reference Laboratory for Campylobacteriosis, Utrecht, The Netherlands
e-mail: j.wagenaar@uu.nl

D. G. Newell
School of Veterinary Medicine, University of Surrey, Guildford, UK
e-mail: diane.newell@btinternet.com

R. S. Kalupahana
Department of Veterinary Public Health and Pharmacology, Faculty of Veterinary Medicine and Animal Science, University of Peradeniya, Peradeniya, Sri Lanka
e-mail: rskalupahana@vet.pdn.ac.lk

L. Mughini-Gras
Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
e-mail: lapo.mughini.gras@rivm.nl

A. Sing (ed.), *Zoonoses: Infections Affecting Humans and Animals*,
https://doi.org/10.1007/978-3-030-85877-3_6-1

Abstract

Campylobacteriosis is a frequently diagnosed disease in humans. Most infections are considered foodborne and are caused by *Campylobacter jejuni* and *C. coli*. The animal reservoirs of these *Campylobacter* species, and the sources and routes of transmission, are described and discussed in this chapter. Most warm-blooded animals can be colonized by *Campylobacter,* but avian species, and in particular poultry, are preferred hosts. Much of the world's poultry production is colonized by *Campylobacter.* Source attribution studies estimate that 20–40% of cases are attributed to the handling and consumption of chicken meat, while up to 80% of cases are due to *Campylobacter* found in the chicken reservoir. The difference suggests that routes other than through the food chain, i.e., environmental contamination, are important. The epidemiology of infections in humans differs between industrialized and low- and middle-income countries. Thus, the most effective interventions would be targeted to primary production. To date, only improved biosecurity is available. If effectively implemented, strict biosecurity can reduce the number of *Campylobacter*-positive flocks, but implementation to this level has proved difficult for the poultry industry. Available interventions in chicken processing plants can substantially reduce *Campylobacter* numbers on carcasses and consequently reduce the risk to humans. Public health strategies therefore utilize control programs, which aim at reducing the level of *Campylobacter* by measures along the food chain. It is now recognized that commercially acceptable complementary interventions for primary production, such as vaccines and feed additives, are urgently needed. Once *Campylobacter* in poultry is controlled then other minor sources of *Campylobacter* including contaminated drinking water, direct contact with (pet) animals, and other food items (e.g., red meat and milk) can be addressed.

Keywords

Campylobacter · Food borne disease · Poultry · Livestock · Source attribution · Environment · Low- and middle-income countries

Campylobacteriosis: The Disease and Its Burden in Humans

Human campylobacteriosis is primarily caused by *Campylobacter jejuni* (*C. jejuni*) and to a much lesser extent by its close relative *Campylobacter coli* (*C. coli*). Human infection with either pathogen largely presents as gastrointestinal illness (Gillespie et al. 2002). *C. jejuni* and *C. coli* together account for more than 90% of all cases of human campylobacteriosis. Infections with other *Campylobacter* species may also occur, but they occur in either specific risk groups, for example, people with impaired immunity (e.g., *C. fetus*) (Wagenaar et al. 2014), or are very rare (e.g.,

C. lari), or cluster in specific geographical areas (e.g., *C. upsaliensis*) (Man 2011). This chapter will focus on *C. jejuni* and *C. coli*, and hereafter *Campylobacter* refers to these two species only.

Campylobacter is the most commonly reported cause of bacterial infectious intestinal disease (IID). However, disease surveillance programs, which include campylobacteriosis, are largely limited to industrialized countries, such as the United States (USA) and Member States of the European Union (EU) (EFSA and ECDC 2021; CDC 2022a). In industrialized countries, *Campylobacter* is isolated 3–4 times more frequently from patients with IID than *Salmonella* or *Escherichia coli*. However, it is well recognized that underreporting of such diseases is frequent. Adjusting for this, the true prevalence of campylobacteriosis was estimated to be 9.2 million in the EU in 2009 (Havelaar et al. 2013) and 1.3 million in the USA in 2011 (Scallan et al. 2011). Nevertheless, serological evidence suggests that exposure to this pathogen is substantially more frequent (Teunis et al. 2013), such that based on serological data virtually all individuals have been exposed to the organism by 20 years of age (Ang et al. 2011) and that the average infection pressure is estimated at around 1.6 *Campylobacter* infections per person/year (Monge et al. 2018). Such exposure can lead to protective immunity, which might affect the outcome and impact on disease incidence and could explain the low reported prevalence of disease in developing countries despite obvious regular exposure (Havelaar et al. 2009).

There are some additional interesting epidemiological features of campylobacteriosis, many of which have yet to be fully explained. These include a seasonal peak, which varies between countries and seems to be inconsistent with seasonal peaks observed in potential sources (Djennad et al. 2019).

In the past campylobacteriosis was largely considered a mild illness, but the severity of this disease is clearly reflected in the relatively high rate of *Campylobacter*-infected individuals seeking medical attention. Surveys show that one in four cases in the Netherlands and one in seven cases in the United Kingdom (UK) visit a general practitioner and approximately 1% of these individuals are hospitalized (Tam et al. 2012; Havelaar et al. 2012). In the acute phase, campylobacteriosis is primarily characterized by gastrointestinal symptoms, such as watery (sometimes bloody) diarrhea, abdominal cramps, nausea, vomiting, and fever. The disease is usually self-limiting, lasting a week or less. Antimicrobial treatment is only indicated in severe cases (e.g., bloody diarrhea or systemic infection). However, *Campylobacter* infections can also have serious sequelae, including Guillain-Barré and Miller-Fisher syndromes, reactive arthritis, and functional gastrointestinal disorders, including irritable bowel syndrome (Helms et al. 2006; Doorduyn et al. 2008; Haagsma et al. 2010; Berumen et al. 2021).

The burden of campylobacteriosis has been quantified in terms of disability-adjusted life-years (DALYs), which is a metric of health loss caused by the disease comprising years of life lost by the population due to disability and premature death. The different manifestations of campylobacteriosis were estimated to cause an average disease burden of 3300 DALYs in the Netherlands in 2019, with sequelae accounting for approximately 80% of this burden (Lagerweij et al. 2020). Among foodborne pathogens investigated in the Netherlands, this DALY estimate was the

highest. Similar studies in the USA in 2011 showed *Campylobacter* to cause a burden second only to *Salmonella*, with a cost of illness of $1.7 billion annually (Hoffmann et al. 2012).

Despite the relative importance of campylobacteriosis, unlike for salmonellosis, there have been no effective intervention programs implemented, with the exception of Iceland and New Zealand where very specific conditions prevailed (Stern et al. 2003; Sears et al. 2011). This is all the more surprising given that the incidence of human campylobacteriosis increased significantly during the 1980s–1990s, stabilized around the start of this century, and has tended to increase again in the second decade of this century in the USA, while remaining stable in Europe (EFSA and ECDC 2021; CDC 2022b). There has been a remarkable sudden decrease in human campylobacteriosis associated with the COVID-19 pandemic in the USA and Europe, as observed also, for example *Salmonella* (Mughini Gras et al. 2021a). The reasons for the lack of specific intervention for *Campylobacter* are debatable, but include the complexity of foodborne and environmental sources and transmission routes, the financial imbalance accruing from interventions where the cost is to the poultry industry while the benefit is to the public health sector, and lack of consumer/political acceptance of effective measures like irradiation or chemical decontamination. In addition, there is a general lack of public interest, which is in part due to the scarcity of major outbreaks.

Characteristics of *Campylobacter*

Campylobacter comprises a genus of Gram-negative, motile, non-spore forming, mostly microaerophilic, spiral bacteria (diameter 0.2–0.5 μm, length 0.5–8 μm). To date (January 2023), the genus includes 43 species (https://lpsn.dsmz.de/genus/campylobacter) and with the use of molecular approaches, this number is rapidly expanding. Both *C. jejuni* and *C. coli* are thermophilic, showing optimal growth at 42 °C. For the purposes of isolation this thermotolerance, especially in combination with resistance to cephalosporin, is often used to reduce contaminating flora and improve recovery, particularly from fecal material.

Campylobacter readily generates resistance against an increasing number of classes of antimicrobials. Although antimicrobials are infrequently prescribed for campylobacteriosis, such resistance can have clinical consequences. There are clear differences in antimicrobial resistance in different geographical areas. Generally, resistance is higher in Asia and Africa compared to Europe, the USA, and Australia and New Zealand (Nhung et al. 2016; Gahamanyi et al. 2020; EFSA 2021). This parallels the amount of antimicrobials used in animals and humans in these regions. Resistance to fluoroquinolones and tetracyclines is increasing in most regions of the world. An association between the licensed use of fluoroquinolones in poultry and increased fluoroquinolone resistance in strains isolated from humans was noticed in the 1980s (Endtz et al. 1990). This association was strengthened by a low fluoroquinolone resistance in *C. jejuni* isolates from humans in Australia, a country where fluoroquinolones were never licensed for use in production animals (Cheng et al. 2012).

Campylobacter is sensitive to many environmental stresses, including desiccation, heat, ultraviolet radiation, atmospheric oxygen, and high salinity. As a consequence, *Campylobacter* is unable to grow naturally outside a host and is considered generally fragile compared with, for example, *Salmonella*. Nevertheless, *Campylobacter* can survive in the environment for prolonged periods, especially in moist conditions. Survival has been recorded for up to 3 months in slurries and water contaminated with organic materials (Nicholson et al. 2005) and up to 10 months in manure compost (Douglas Inglis et al. 2010).

The fastidious nature of the organism is reflected in its demanding requirements at culture. Diagnosis of infection is usually based on isolation from fecal samples using selective media, containing appropriate antimicrobials, and incubated under reduced oxygen tension, at 42 °C for 48–72 h. However, the isolation technique and media constituents may vary depending on the matrix under investigation and may affect both the efficacy of recovery and the species and/or strain types recovered (Newell et al. 2001). Numerous rapid detection tests, using a variety of technologies, are now commercially available. For application in food chain settings, e.g., slaughterhouses or chicken farms, such tests need to be cheap and user-friendly as well as sensitive and specific (Llarena et al. 2022).

The typing of *Campylobacter* has proved challenging. The organisms demonstrate considerable variation at both the phenotypic and genotypic levels and many attempts have been used to exploit this diversity to characterize *Campylobacter* for epidemiological studies. Initial typing methods included serotyping and phage typing. However, these methods were largely superseded by molecular techniques, such as *fla*-typing and Pulsed Field Gel Electrophoresis (PFGE) (Wassenaar and Newell 2000). Subsequently, as DNA sequencing became cheaper and quicker, Multi Locus Sequence Typing (MLST), based on variations in the sequences of seven housekeeping genes, was used to establish the population structures of *C. jejuni* and *C. coli* (Dingle et al. 2001). The significant advantage of this technique was its portability due to the use of globally available internet-based databases, which allowed easy strain comparison. Not surprisingly, this technique was quickly exploited for epidemiological purposes and, with the application of highly sophisticated statistical methods, its use was expanded to determine potential infection sources and to provide a global public health tool. Many *C. jejuni* MLST sequence types (STs) have been cataloged to date. Most STs are generalists and can colonize several hosts but some are specialized to defined hosts, such as cattle and chicken (Mourkas et al. 2020). However, the use of just the sequences of seven housekeeping genes has raised issues regarding resolution for the purpose of source identification. With continued improvements in DNA sequencing, rapid whole-genome sequencing (WGS) of campylobacters has become routine (Didelot et al. 2012). However, due to the high genome diversity of *Campylobacter*, SNP-based comparisons are problematic. In 2017, a core-genome MLST (cgMLST) approach was proposed expanding the number of gene sequences analyzed to 1343 (Cody et al. 2017). The cgMLST typing approach has now been validated and types present in a wide range of animals identified (Hsu et al. 2020) and compared with those found causing human disease using increasingly sophisticated analytical techniques, including machine learning

techniques (Arning et al. 2021). Nevertheless, the large number of "generalist" sequence types continue to elude source attribution. As a consequence, efforts to further improve the resolution by incorporating additional sequences, for example, from potential host-associated genes, continue.

The Disease and Carriage in Animals

The primary habitat of *Campylobacter* and its main amplification site is the intestinal tract of warm-blooded animals. Both *C. jejuni* and *C. coli* are normal inhabitants of the guts of healthy livestock, pets, and wild animals. There appears to be some host preference with *C. jejuni* more commonly isolated from most animals, like cattle, dogs. and cats, while pigs predominantly carry *C. coli*. The reason for this is unclear. Certainly, a significant proportion of livestock animals is colonized and the prevalence varies with factors like age, husbandry, country, etc. (Plishka et al. 2021; Mota-Gutierrez et al. 2022; Knipper et al. 2022). Similarly, up to 45% of dogs are colonized (Marks et al. 2011).

The role of *C. jejuni* and *C. coli* as pathogens in these animals is considered of relatively minor importance. They can cause abortion in cattle and sheep, but are usually less frequently isolated from aborted fetuses than *C. fetus*. An exception is the spread of a single tetracycline-resistant *C. jejuni* clone causing abortion in sheep throughout the USA (Wu et al. 2014). This hypervirulent clone is also reported in other countries such as the UK, Japan, and China (Stone et al. 2014; Wu et al. 2016, 2020; Sahin et al. 2017; Tang et al. 2017; Hsu et al. 2020; Yaeger et al. 2021a, b). Interestingly, this clone has also been recovered from diarrheic humans in the USA, but the route of transmission has not yet been identified. The role of *Campylobacter* as a pathogen in dogs remains debatable (Burch 2005; Marks et al. 2011). The high level of asymptomatic carriage (Marks et al. 2011) suggests that any association with disease is coincidental rather than causative. Nevertheless, there is certainly evidence of such companion animals as a source for human infections (Mughini Gras et al. 2013, 2021b).

Poultry, in particular and (wild) avian species in general, are the preferred hosts for these organisms. This is a reflection of the bacterium's thermophilic character, as 41–42 °C is the normal body temperature of a bird. Colonization occurs throughout the gut, but primarily in the cecum of a broiler, where levels of up to 10^9 colony forming units per gram have been reported. All the evidence indicates that *Campylobacter* act as a commensal in the avian gut, although this is occasionally disputed. The prevalence of *Campylobacter*-positive broiler flocks varies considerably, for example, with age, season of the year, latitude, extensive or intensive rearing, etc. In an EU-wide survey of broiler flocks undertaken in 2008, the prevalence of *C. jejuni*/*C. coli* colonization varied between 5% and 100% among Member States (EFSA 2010). The prevalence is particularly high if the flocks are free-ranging (Vandeplas et al. 2010). The organism is highly infectious and in each colonized flock up to 100% of birds can be *Campylobacter*-positive. Thus, overall, it is reasonable to assume that a significant proportion of broilers produced worldwide are colonized with these organisms.

Campylobacter Epidemiology in Low- and Middle-Income Countries

Country-specific epidemiological data on infectious enteric diseases, especially those transmitted through the food chain, has been sparse in Low- and Middle-Income Countries (LMIC) but the effects of these diseases, as leading causes of morbidity and mortality, has long been recognized.

Campylobacteriosis is generally considered to be a major contributor to those diseases, especially in young children, but evidence from large global case-controlled studies has been poorly available. There have been multiple barriers to such investigations, including costs, organizational structures, perceptions of importance, etc. One barrier has been access to modern rapid diagnostic/surveillance technologies. For example, qPCR can have twice the sensitivity of *Campylobacter* detection than the more conventional culture methods generally available in laboratories in LMIC (Liu et al. 2016). Recently, the microbiological causes of diarrheal diseases in LMIC have been investigated in two such global studies using improved diagnostic and statistical tools. In the Global Enteric Multicentre Study (GEMS), the etiology and population-based burden of pediatric diarrheal disease in Sub-Saharan Africa and South Asia were investigated (Kotloff et al. 2013) in 9439 children with moderate-to-severe diarrhea and 13,129 children without diarrhea. Interestingly *C. jejuni* was only identified as a statistically significant cause of pediatric diarrhea in children of 0–11 months and 24–59 months in sites in India. Five other enteropathogens, including rotavirus and *Cryptosporidia*, were considered substantially more important targets for intervention. However, when qPCR was applied rather than more conventional methods, *Campylobacter* was identified as the sixth most common cause of illness. Similarly, the Malnutrition and Consequences for Child Health and Development (MAL-ED) consortium study (Platts-Mills et al. 2015), comparing 7318 diarrheal and 24,310 non-diarrheal stools from 2145 children (aged 0–24 months) from eight sites in South America, Sub-Saharan Africa, and Asia indicated that *Campylobacter* was among the most important causes of pediatric diarrhea, especially in the second year of life. These recent epidemiological surveys support reports from the WHO's Foodborne Disease Burden Epidemiology Reference Group (FERG), which considers *Campylobacter* one of the most common organisms causing diarrhea, especially in children (Havelaar et al. 2015), with the geographical regions most highly affected by campylobacteriosis in LMIC.

These recent large epidemiological studies have also confirmed some differences in the presentation of campylobacteriosis between high- and low- and middle-income countries. For example, although it had been previously well recognized that in LMIC adults excreting *Campylobacter* are usually asymptomatic, many infected children also show no symptoms. In addition, the seasonal distribution in *Campylobacter* infections generally seen in the higher income world is not observed elsewhere (Havelaar et al. 2015; Platts-Mills et al. 2015).

The extent of the public health burden due to campylobacteriosis in LMIC is only just begun to be understood. Not only are symptomatic *Campylobacter* infections associated with poor linear growth in children over the first 2 years of life (Amour

et al. 2016; Rogawski et al. 2018), but repeated exposure to such enteropathogens, even if subclinical, can cause substantial enteric dysfunction and malnutrition (Walson and Pavlinac 2018). Such life changing effects reinforce calls for interventions against foodborne enteropathogens, including *Campylobacter*, in LMIC (WHO 2017). Another potentially significant health issue is Guillain–Barré syndrome (GBS), which is most commonly caused by a preceding *Campylobacter* infection. Unfortunately, data on post-infectious GBS in LMIC is sparce and largely confined to South Asia (Bangladesh and India) (Papri et al. 2021).

Worldwide, the control and prevention of the public health burden of campylobacteriosis requires surveillance and monitoring especially of *Campylobacter* throughout the food chain. Unfortunately, LMIC rarely include foodborne enteropathogens, such as *Campylobacter,* in disease surveillance (Deolalikar et al. 2021). As a consequence, the national prevalence of such diseases in the population is generally unknown. Among South-East Asian countries in 2017, apparently only Singapore included campylobacteriosis in its national disease surveillance program (Premarathne et al. 2017).

The sources and routes of *Campylobacter* transmission in LMIC are poorly understood. Although epidemiological data from Africa, Asia, and the Middle East are incomplete, it is widely accepted that infection with *Campylobacter* is endemic in these regions, and traveling to Asia, Africa, Latin America and the Caribbean, and Southern Europe poses an increased risk of campylobacteriosis compared to traveling within Western Europe (Mughini Gras et al. 2014). It is generally believed that in such countries, campylobacteriosis is limited to children, because exposure in early life leads to protective immunity (Havelaar et al. 2009), which would also be consistent with endemicity.

The prevalence of human campylobacteriosis in LMIC may be attributed to many factors, including poor food hygiene, environmental contamination, animal rearing and handling practices, wet markets, etc. In high-income countries, human-to-human transmission is not considered an important route of *Campylobacter* infection, except in some institutional situations. Nevertheless, high levels of asymptomatic infections in those locations where sanitary facilities are inadequate could contribute to environmental contamination and result in higher exposure.

Campylobacter is generally considered a foodborne enteropathogen. To date, there is very little information available on potential sources of infection in LMIC and the little available data comes primarily from poultry, presumably because this is considered the primary source in high-income countries. Poultry production is thriving in South-East Asia, with livestock production in these regions being largely extensive (Gilbert et al. 2015), but frequently also as backyard or small local units for economic reasons (Alders et al. 2018). In such systems, biosecurity is either unfeasible or very difficult to apply (Kalupahana et al. 2013; Wang et al. 2015). Even commercial poultry production will use deep litter open-house systems where biosecurity is minimal and the birds are constantly in contact with the outdoor environment, wild animals, and insects. Moreover, new flocks, including day-old chicks, are generally exposed to already *Campylobacter*-colonized chickens in the same farms (Kottawatta et al. 2017). Therefore, a high prevalence of *Campylobacter*

colonization of broilers at slaughter in LMIC should be expected. Consistent with this, surveys conducted in Sri Lanka have reported >65% *Campylobacter* prevalence in broilers at slaughter (Kottawatta et al. 2017; Kalupahana et al. 2018).

Published surveys of *Campylobacter* contamination in retail poultry meats and their by-products (such as ground or frozen poultry meats) indicate that in most countries, regardless of social-economic status, the majority of samples are contaminated with *Campylobacter* (Suzuki and Yamamoto 2009) and there is no obvious difference between countries in the prevalence of sample contamination. However, few such retail surveys have been undertaken in LMIC compared to high-income countries.

Because *Campylobacter* is a common gut colonizer of many domestic animal species, not just poultry, multiple attributable sources and routes of transmission can occur especially in those countries where animal-to-human contact levels might be high. For example, in India *Campylobacter* colonization is frequent in dogs and calves, as well as poultry (Begum et al. 2015), though whether these strains can cause human disease is not known (Begum et al. 2015). To understand the attributable role of potential sources, time-related strain collections from humans and animals/environment need to be compared using typing techniques of appropriate discriminatory power, such as WGS. Unfortunately, such techniques may not be widely available in LMIC and, because of their low discriminatory power, little if any, useful conclusions can be drawn on sources from the use of low-technology techniques, such as serotyping (Bodhidatta et al. 2013).

Effective cheap and easy-to-apply interventions for the control and prevention of campylobacteriosis remain a major challenge for LMIC, where food chain regulations would be difficult to implement. Nevertheless, the eating and handling of raw or improperly cooked poultry meat has been shown to be the most common source of human campylobacteriosis throughout the world. One (apparently) simple approach, therefore, is education to encourage the effective cooking of poultry meat. In Sri Lanka, the absence of *Campylobacter* contamination in chicken curries (Kulasooriya et al. 2019) indicated that such approaches were effective. However, *Campylobacter* contamination of chicken dishes identified in, both local and branded, Pakistani restaurants (Arshad and Zahoor 2019) indicate that kitchen hygiene is also important.

Overall, the paucity of information available on the epidemiology of campylobacteriosis in LMIC highlights the need for active food safety surveillance in these countries using state-of-art technologies and approaches.

Sources and Transmission Pathways of Human Campylobacteriosis

Although *Campylobacter* is considered mainly a foodborne pathogen, there is evidence for other transmission pathways, including contact with colonized animals and environments contaminated by their waste products, as well as, rarely, infected people in conditions of poor hygiene (Mughini Gras et al. 2012, 2013, 2014, 2021b). It is well recognized that *Campylobacter*-containing gut contents can enter the food chain by contaminating various food products of animal origin, including meats and

dairy products. Cross-contamination during food preparation at home is also an important transmission route (Bai et al. 2021). Alternative routes with animals as sources include exposure to environments contaminated by primary production (e.g., run-off from livestock in farms and at pasture, water used for cleaning animal-containment areas, stockpiled sewage, etc.). *Campylobacter* survives for long periods in surface waters, so such contamination might pose a risk to humans through the drinking of untreated water, recreational activities, or the consumption of fresh produce irrigated or washed with manure-contaminated water.

Campylobacter Source Attribution

A general framework for source attribution of campylobacteriosis has been designed (Wagenaar et al. 2013). Based on this framework, animals (e.g., cattle, sheep, poultry, etc.) are defined as *reservoirs* or *amplifying hosts*; the environment, the food chain, and direct contact with animals are given as examples of *pathways*; drinking water, meat, milk, and occupation are given as examples of *exposure*; and examples of *risk factors* include swimming in rivers, eating chicken meat, beef, etc. In a typical example, cattle (reservoir) may contaminate the food chain (pathway) resulting in a hazard in the milk supply (exposure), which manifests itself as an increased risk associated with the consumption of unpasteurized milk (risk factor) (Wagenaar et al. 2013).

Source attribution models provide an estimate of the relative contribution of the different known reservoirs to the burden of human illness. They can be used to inform decision makers in order to target the most effective intervention strategies and are, therefore, an important tool for risk management (Pires et al. 2009). Several approaches can be used for source attribution, including microbiological (e.g., microbial subtyping) and epidemiological (e.g., outbreak investigations and case-control studies) approaches and intervention studies (Pires et al. 2009). Structured expert opinions and comparative exposure assessment can also be used for source attribution, but will not be considered here.

Source Attribution Based on Outbreak Data

Most *Campylobacter* infections are sporadic. As an example, in Europe in 2019, the total number of reported campylobacteriosis cases was 220,682, of which only 1254 were related to outbreaks (EFSA and ECDC 2021). Outbreak data is, therefore, generally considered of limited value for campylobacteriosis because of the rarity of reported outbreaks (Pires et al. 2010). *Campylobacter* outbreaks, however, may occur more frequently, but are often unreported due to the generally intermittent typing of clinical isolates. Indeed, the added value of high-throughput sequencing methods for campylobacteriosis outbreak investigation has been shown in several occasions, such as during the large waterborne campylobacteriosis outbreaks that occurred in New Zealand, in 2016 (Gilpin et al. 2020). An estimated 6260–8320 campylobacteriosis cases were linked to the contamination of an untreated, groundwater-derived drinking water supply. Of the 12 different *Campylobacter*

genotypes observed in the clinical cases, four were also retrieved from water, three from sheep, and one from both water and sheep. The outbreak was traced back to contamination of the water supply after a heavy rainfall event that caused drainage of sheep feces into a shallow aquifer. The existence of a routine clinical surveillance for campylobacteriosis, coupled with early testing of water for pathogens and genotyping of *Campylobacter* isolates from human cases and potential sources, facilitated outbreak detection and helped define its source, as well as confirm outbreak periods and cases. Similar experiences are increasingly being documented for foodborne campylobacteriosis outbreaks as well (Sorgentone et al. 2021). Moreover, using data of the New Zealand outbreak, it has been shown that alternative data sources (i.e., general practitioner consultations, consumer helpline, Google Trends, Twitter microblogs, and school absenteeism) can provide earlier indications of the outbreak as compared to conventional case notifications (Adnan et al. 2020). Routine application of WGS to *Campylobacter* isolates is already a reality in several governmental agencies, industry, and academia. The ever-growing availability of sequencing data as well as the creative exploitation of alternative data sources are expected to improve our ability to detect and characterize *Campylobacter* outbreaks, including source tracing and root cause determination of contamination events (Franz et al. 2016).

Although scarce, campylobacteriosis outbreak data is collected annually in Europe and has been used to estimate the causative vehicles for the years 2005–2006 (Pires et al. 2010). Putative sources rank differently depending on whether the data was analyzed in terms of either the proportion of outbreaks or the proportion of infected individuals reported. The majority (~64%) of outbreaks had no identified source, while ~12% were attributed to meat products as a whole and ~10% specifically to chicken. In contrast, in terms of ill individuals, the majority (~44%) was attributed to travel, ~17% to putatively contaminated drinking water, 10% each to meat and chicken, and 36% were of unknown source. Although the ranking of source importance seems different, chicken remains an important source regardless of the approach taken. Indeed, the authors report that "among illnesses that could be attributed to a source, 29% of campylobacteriosis cases were attributed to chicken" (Pires et al. 2010).

Source Attribution Based on Case-Control Studies

Case-control studies have been used in several countries to identify those risk factors associated with sporadic *Campylobacter* infections. Overall, these studies indicate that the handling and consumption of chicken meat is a very important risk factor (Doorduyn et al. 2010; Domingues et al. 2012; MacDonald et al. 2015; Mossong et al. 2016; Rosner et al. 2017; Kuhn et al. 2018). Other frequently identified risk factors include the consumption of unpasteurized milk (Friedman et al. 2004; Mughini Gras et al. 2021b), eating in restaurants (Friedman et al. 2004; Danis et al. 2009), contact with pet dogs (especially puppies) (Friedman et al. 2004; Doorduyn et al. 2010; Mughini Gras et al. 2013; MacDonald et al. 2015; Mossong et al. 2016; Kuhn et al. 2018), contact with livestock (Friedman et al. 2004; Danis et al. 2009; Mughini Gras et al. 2012; Rosner et al. 2017), and foreign travel

(Friedman et al. 2004; Doorduyn et al. 2010). The calculations of the attributable fractions for each risk factor also indicate that, like the outbreak data, chicken consumption accounts for 28–31% of sporadic cases (Doorduyn et al. 2010; MacDonald et al. 2015; Rosner et al. 2017; Kuhn et al. 2018). In contrast, the contribution of dog ownership is 4–8% (Doorduyn et al. 2010; MacDonald et al. 2015), but it can go up to 21% in children under 5 years (Kuhn et al. 2018). Of course, many factors can influence source attribution studies using case-control data. For instance, individuals taking proton-pump inhibitors or having a chronic gastrointestinal disease have increased risk of campylobacteriosis (Doorduyn et al. 2010; Mughini Gras et al. 2012; Rosner et al. 2017; Kuhn et al. 2018; Fravalo et al. 2021), probably as a consequence of reduced gastric acidity allowing the survival of *Campylobacter* during passage through the stomach and/or disturbed gut function facilitating intestinal infection.

A recent systematic review and meta-analysis (Fravalo et al. 2021), which synthesized the evidence provided by 71 eligible case-control studies on risk factors for sporadic *Campylobacter* infection, highlighted the importance of other, less common risk factors beyond chicken consumption. These include consumption of food products like beef, eggs, and dairy, especially when consumed raw/undercooked, but also non-foodborne transmission routes like contact with animals and environmental sources. For example, occupational exposure to animals or products thereof, such as working in a slaughterhouse, farm, pet shop, or zoo, as well as working in food handling/preparation, emerged as significant risk factors. The same applied to (non-occupational) contact with farm animals, wild animals and pets, and environmental exposure to playground sandpits, rural environments, or recreational waters, with these non-foodborne risk factors, as well as person-to-person transmission, being particularly important among children (Fravalo et al. 2021).

Specific immunity against *Campylobacter,* acquired as a result of prior exposure, is another very important confounder of case-control studies (Havelaar and Swart 2016). Certainly, repeated exposure to pathogens, such as *Campylobacter*, may lead to sufficient immunity to provide protection against severe clinical illness (Swift and Hunter 2004). Such immunity can lead to individuals being protected from disease, even when colonized (Havelaar et al. 2009; Havelaar and Swart 2016), and this has been proposed as an explanation of why, in some instances, the regular consumption of poultry meat (at home) is identified as a protective, rather than a risk factor (Friedman et al. 2004). Acquired immunity also provides an explanation of why either the very frequent consumption of chicken meat or never consuming it, are risk factors for campylobacteriosis (Mughini Gras et al. 2021b). Indeed, people who frequently consume chicken are highly exposed to chicken-associated *Campylobacter* strains and therefore are at increased risk of falling ill with these strains because the levels of exposure to these strains are too high to allow acquired immunity to exert any protective effect. Conversely, people who do not eat chicken meat would not be exposed to these strains at all, and therefore would be unable to develop any immunity against them, thereby falling ill more easily upon incidental exposure to them via, e.g., cross-contamination of other food items or non-foodborne transmission. It has also been shown that consumption of chicken meat is a risk factor for

campylobacteriosis only or predominantly when this is consumed outside the household (Swift and Hunter 2004; Friedman et al. 2004; Mossong et al. 2016; Lake et al. 2021), which indicates that exposure to chicken-associated *Campylobacter* strains outside the household (e.g., at restaurants, catering events, etc.) would increase the chance of being exposed to (possibly higher doses of) specific *Campylobacter* strains different from those to which people are (usually) exposed at home (Mughini Gras et al. 2021b).

Source Attribution Based on Microbial Subtyping

As previously indicated, *Campylobacter* are highly phenotypically and genotypically variable. This variability has been exploited to develop subtyping strategies with the aim of determining sources of human infection. However, for various reasons including the high plasticity of the *Campylobacter* genome, the lateral transfer of genetic material among strains, the time delay to diagnosis, and the poor recovery from putative sources, the direct tracking of strains from source to human has not been feasible. However, the widespread application of MLST, as well as other genotyping methods with higher discriminatory power like cgMLST, allowed for the study of *Campylobacter* population structures and the conduction of source attribution analyses. Studies of the evolutionary relationships within populations reported that some *Campylobacter* strain features are preferentially associated with certain animal hosts. Thus, using complex statistical methods, the probable sources can be inferred by comparison of the *Campylobacter* strains recovered from diseased humans with those recovered from a range of animal, food, and environmental sources. Several MLST-based studies, reviewed by Cody et al. (2019), have provided in the past the first source attribution results for campylobacteriosis, showing that most (50–80%) strains infecting humans come from the chicken reservoir, 20–30% from cattle, and the remainder from other reservoirs (e.g., sheep, pigs, wild animals, etc.) (EFSA BIOHAZ 2010). However, in more recent years, the growing availability of WGS data allowed for genomic data with a much higher discriminatory power than MLST, such as cgMLST and wgMLST, to be used in source attribution studies (Pérez-Reche et al. 2020; Lake et al. 2021; Mughini Gras et al. 2021b; Harrison et al. 2021; Arning et al. 2021). While most human cases are still attributed to poultry, followed by cattle, the ability to better differentiate isolates based upon more than just seven MLST genes, coupled with the use of more powerful models, allow for more accurate attribution estimates. This includes better differentiation of host generalist, commonly occurring or clonally related strains.

While there is an apparent conflict between the importance of poultry as a source from case-control studies (20–40%) and from the genotyping studies (50–80%), this is explained by case-control studies being able to trace human cases back only to the level of exposure (e.g., food items consumed, contact with animals, etc.), while genotyping data indicates the original host reservoir. It has been hypothesized that the difference reflects that *Campylobacter* strains may reach humans through pathways other than food, for example, through environmental exposure (EFSA BIOHAZ 2010) (section "Role of the Environment").

Intervention Studies

On the presumption that poultry is the major source of sporadic campylobacteriosis, there have been several incidents that have acted as "natural experiments," which have been investigated to determine the effect of reduced population exposure to *Campylobacter* in the food chain. For example, in 1999, contamination of animal feed with dioxin in Belgium resulted in a nationwide withdrawal of broiler meat from the market, which was concomitant with a 40% decrease in campylobacteriosis, countrywide (Vellinga and Van Loock 2002). Similarly, in 2003 in the Netherlands, an avian influenza outbreak led to a massive poultry cull, which was associated with a subsequent 30% decrease overall in campylobacteriosis (Friesema et al. 2012). This disease reduction varied between regions from 10% to 70%, with the largest fall reported in those laboratories' serving areas where the flocks were actually culled. This observation supports the hypothesis that there were important transmission routes other than the handling and consuming poultry meat (EFSA BIOHAZ 2010; Friesema et al. 2012). As yet, the transmission routes of such alternative pathways are unclear.

Other interventions targeted at the poultry production sector and/or to the poultry meat consumer, resulted in reduced exposure to national populations in Iceland and New Zealand. Following these interventions, the number of reported campylobacteriosis cases fell by 72% in Iceland (Stern et al. 2003) and by 54% in New Zealand (Sears et al. 2011). Furthermore, in New Zealand there was a concurrent 74% reduction in the proportion of poultry-associated campylobacteriosis cases as determined by source attribution using MLST (Sears et al. 2011) and 13% decline in hospitalizations for Guillain-Barré syndrome (Baker et al. 2012).

Role of the Environment

Campylobacter is often found in the environment, including surface water, where it usually indicates recent fecal contamination from animals, sewage, or agricultural run-off. *Campylobacter*'s fate in the environment is typically the one of die-off rather than growth. Although *Campylobacter* survives poorly outside the host, some specialist strains can survive better in certain sylvatic (Hepworth et al. 2011), farmland (French et al. 2005), and environmental (French et al. 2005; Sopwith et al. 2008; Colles et al. 2011) niches. These strains are generally more resistant to physical stress (Sopwith et al. 2008). *Campylobacter* can also assume a viable, but non-culturable state in response to advert conditions outside the host (Murphy et al. 2006).

Human *Campylobacter* infections of environmental origin exhibit strong seasonality (Mughini Gras et al. 2012). Indeed, *Campylobacter* survival in the environment is compromised by factors like high temperatures and sunlight, among others, and shedding from animals varies seasonally depending on stress, changes in diet, housing conditions, rearing period, etc. Moreover, the pattern of human exposure to environmental sources (e.g., outdoor activities) is largely weather-dependent. Although the primary transmission route for human *Campylobacter* infection is

contaminated food, source attribution studies have estimated that on top of the contributions of livestock and wild animals, the environment may account for a further 5–10% of human campylobacteriosis morbidity, with open water swimming, consuming game meat, and exposure to storm water overflows being a source of environment-borne campylobacteriosis (Mughini Gras et al. 2012, 2021b; Sales-Ortells et al. 2015; Mossong et al. 2016). Studies have also shown that heavy rainfall may lead to *Campylobacter* entering the drinking water supply system (Gilpin et al. 2020). Perhaps more importantly, water may act as a source for *Campylobacter* (re)colonization in livestock (Bull et al. 2006). Yet, the environment at large serves more as a vehicle of transmission for *Campylobacter* among animals, from animals to humans and vice versa, rather than as an amplifying reservoir per se.

Surface water represents a "sink" that collects *Campylobacter* strains from different (animal) hosts, whose individual contributions have been quantified in source attributions studies based on MLST (Mughini Gras et al. 2016) and cgMLST (Mulder et al. 2020). This latter study, conducted in the Netherlands, provides the most comprehensive data on the prevalence, genotypes, and animal sources of *Campylobacter* in surface water. Prevalence is the highest in agricultural waters (77%) and in autumn and winter (74%), and lowest in recreational (swimming) waters (46%) and in summer (54%), which concurs with *Campylobacter* being highly sensitive to sunlight and high temperatures. Overall, water isolates are mainly attributed to wild birds (84%) and poultry (10%). However, the probability for water isolates to originate from poultry is significantly higher in high poultry density areas, i.e., a geographical association exists between the magnitude of the local poultry industry and its role as source of microbial contamination of the environment. Similarly in the USA, it has been shown that communities with high-density poultry operations have higher incidences of campylobacteriosis and infectious diarrhea (Poulsen et al. 2018).

Campylobacter in Poultry and Intervention in Primary Production

Given that the majority of the infecting strains in humans come from chicken, targeting *Campylobacter* in poultry production has become the preferred public health measure (Koutsoumanis et al. 2020). The poultry meat chain can be viewed as two distinct stages: chicken rearing and production (largely on-farm to entry to the slaughter house) and poultry meat processing (largely lairage to retail). Theoretically, control measures focused on the primary production stage will prevent up to 80% of human cases, by preventing or reducing *Campylobacter* entering the food chain and the environment, while those measures targeted at the processing stage, can prevent only an estimated 42% of cases (Mughini Gras et al. 2012). Control of *Campylobacter* in primary poultry production, however, has proved to be very difficult (Wagenaar et al. 2013).

Campylobacter colonization occurs in all types of commercially produced poultry (e.g., broilers, turkeys, ducks) (Wagenaar et al. 2006), but clearly the focus for intervention is broiler, as it forms the largest source of human infections. The

prevention of *Campylobacter* in poultry is solely targeted at meat-producing birds. This is because vertical transmission is extremely rare, if at all (Callicott et al. 2006; Cox et al. 2012). Thus, each new broiler production cycle starts with *Campylobacter*-free chicken. In all-in/all-out production systems, poultry houses are cleaned, disinfected, and dried before the arrival of a new flock. Such preparation seems to be largely effective at preventing the carry-over of *Campylobacter* from previous flocks (Newell et al. 2011; Georgiev et al. 2017). Nevertheless, birds subsequently become colonized with the bacteria. Experimental studies indicate that the ingestion of as few as 40 organisms can cause colonization (Cawthraw et al. 1996). Once the first bird has been colonized, it sheds large numbers of bacteria in its feces (up to 10^7 cfu per gram), and most, if not all, the other birds in the flock become colonized within a few days. Thus, preventing the first bird becoming colonized seems to be a prerequisite for a *Campylobacter*-negative flock.

Broiler flocks are frequently exposed to the *Campylobacter* from their external environment throughout their limited lifespan (Newell et al. 2011). However, colonization does not usually become detectable until 2–3 weeks of age of the flock. This so-called "lag-phase" appears to be due to an inherent resistance in young chickens (Kalupahana et al. 2013) which is, at least in part, a result of maternal immunity (Cawthraw and Newell 2010).

By comparing *Campylobacter*-negative with -positive flocks, many risk factors and farm practices have been identified, which increase the chance of flock positivity (Newell et al. 2011; Sibanda et al. 2018). One major risk factor is the age of broilers at slaughter, which is most likely associated with exposure to external contamination over time and is a measure of the effectiveness of biosecurity. Other biosecurity-associated risk factors, such as multiple broiler houses on the farm, the presence of other livestock, partial depopulation (thinning), pets on the farm, etc., are also important. Nevertheless, no one biosecurity-related factor seems to predominate. Moreover, although improved biosecurity can decrease the risk of a flock becoming *Campylobacter*-positive, it seems that even strict biosecurity cannot guarantee a *Campylobacter*-free flock at the time of slaughter (Newell et al. 2011). In many countries, the biosecurity challenge seems even more difficult in the summer months, when the prevalence of *Campylobacter*-positive flocks increases significantly in response to some temperature-related factors (Jore et al. 2010). Some of this seasonal increase may be associated with transmission by flies. In Denmark, this risk has been significantly reduced by the application of fly-screens around broiler house ventilation systems (Bahrndorff et al. 2013). The efficacy may be country-dependent, i.e., related to weather conditions, as well as dependent on the biosecurity level already applied.

In Europe, improved biosecurity has been strongly recommended as the only currently available intervention measure to reduce flock positivity (Koutsoumanis et al. 2020). However, the appropriate targeting of biosecurity measures has proved very frustrating for the poultry industry. Anecdotal evidence suggests the compliance of farmers with general biosecurity measures is essential and such compliance would be even more important in summer months (Koutsoumanis et al. 2020). The challenge is likely to become even greater in the future given consumer-driven

concerns for animal welfare leading to an increasing trend toward the production of slower-growing animals with a longer lifespan and with outdoor access. Under such conditions good biosecurity is impractical (Kalupahana et al. 2013).

It is widely recognized that biosecurity alone cannot produce *Campylobacter*-negative flocks and that complementary measures will be required to increase the resistance to, or reduce the colonization of, birds with the bacterium (Koutsoumanis et al. 2020; Lu et al. 2020). Research into vaccination against *Campylobacter* is progressing, but not yet ready for practice (de Zoete et al. 2007; Nothaft et al. 2021). Neither is it yet possible to influence the intestinal flora to generate a *Campylobacter*-resistant avian gut (Schneitz 2005). The use of bacteriophages and bacteriocins looks promising (Wagenaar et al. 2005), but research to solve key issues in safety, efficacy, and sustainability is still needed (Olson et al. 2021). The use of medium chain fatty acids has been reported to have at least some effect on *Campylobacter* colonization (van Gerwe et al. 2010; Hermans et al. 2012; Jansen et al. 2014; Guyard-Nicodème et al. 2016), but the results require validation in the field.

Thus, it currently seems that improved biosecurity is the only credible measure available to decrease the prevalence of *Campylobacter*-positive flocks. However, as indicated above, the identification of specific and effective biosecurity approaches has proved very difficult. Thus, a wide range of high-level biosecurity measures need to be consistently maintained throughout the life of intensively reared flocks. This is often impractical, especially when *Campylobacter* colonization is asymptomatic, and therefore with no consequent economic loss to providing an incentive for the poultry farmer.

Post-Harvest Control Measures in Poultry

When *Campylobacter* colonization cannot be prevented at the farm level, post-harvest treatment becomes very important. Such treatments include the prevention of cross-contamination and the application of chemical or physical methods of decontamination in the slaughterhouse. The availability and effectiveness of such methods, with particular relevance to Europe, have been reviewed previously (Koutsoumanis et al. 2020).

Cross-contamination can be a significant problem associated with the huge throughput of carcasses (circa 13,000 per hour in many processing plants), slaughter line automation, and the high concentrations of *Campylobacter* in cecal contents. Any leakage of fecal material, or rupture of the gut during evisceration, can lead to surface contamination of the meat. Interestingly, there are statistically significant differences, in the level of carcass contamination between slaughterhouses (EFSA 2010), suggesting that some processing plants are better than others at controlling this problem. However, the basis of these differences has yet to be determined (Koutsoumanis et al. 2020).

The decontamination of carcasses with chemicals is allowed in the USA and currently practiced using several chemicals, such as organic acids, quaternary ammonium compounds, acidified sodium chlorite, and trisodium phosphate.

Although the decontamination of carcasses with chemicals is allowed in the EU, specific approval is required and currently no chemic decontaminants have been approved for use on chicken carcasses.

Some physical treatments (e.g. ,ultraviolet, ultrasound, etc.) have been specifically applied to reduce *Campylobacter* on chicken carcasses, but their effectiveness is usually limited to a reduction of only 1–2 $\log_{10}$. Highly effective irradiation procedures are poorly accepted by consumers and difficult to implement under high throughput conditions. The freezing of carcasses from positive flocks can reduce *Campylobacter* concentrations by 2–3 $\log_{10}$ and this strategy has been effectively used in Iceland as part of a program to reduce human campylobacteriosis (Stern et al. 2003). However, from both the logistic and the economic (i.e., the preference of consumers for fresh meat) viewpoints, such a strategy would be difficult to implement, especially in those countries with high prevalence of *Campylobacter*-positive flocks (Havelaar et al. 2007).

Interventions and Public Health Impact

The potential public health impact of intervention measures in the poultry production chain are clearly demonstrated in two successful examples from Iceland and New Zealand (see section "Intervention Studies").

In Iceland, multiple-level measures were implemented (including producer and consumer education, enhanced biosecurity, changes in poultry processing, and the identification and freezing of products from *Campylobacter*-positive flocks) in response to a sharp increase in campylobacteriosis in 1999 (Tustin et al. 2011). As mentioned before, this spectrum of measures resulted in a 72% reduction in the incidence of campylobacteriosis (Stern et al. 2003). Of all these measures, the freezing of contaminated products is considered the most important (Tustin et al. 2011). In New Zealand, a 54% reduction in the incidence of campylobacteriosis was similarly achieved as a consequence of the introduction of a range of voluntary and regulatory measures (Müllner et al. 2010; Sears et al. 2011; Baker et al. 2012).

Given these successes, it is tempting to extrapolate those approaches implemented in New Zealand and Iceland to other countries. However, in both cases, specific conditions prevailed and, therefore, success in disease reduction in other countries may not be predictable. While highly effective interventions against *Campylobacter* in broiler farms remain elusive, slaughterhouses in the EU have been set up to keep *Campylobacter* contamination in broiler carcasses under control. Indeed, since 2018, a process hygiene criterion (Commission Regulation EU 2017/1495), with a limit of 1000 CFU/g of neck skin, has been implemented among EU Member States. This limit was based on a Scientific Opinion of the European Food Safety Agency (EFSA) on control options for *Campylobacter* along the poultry meat production chain and their estimated impact on the reduction of the number of human campylobacteriosis cases (EFSA BIOHAZ 2011). The EFSA estimated a public health risk reduction of more than 50% if carcases complied with the aforementioned process hygiene criterion. Moreover, a cost-benefit analysis

indicated that a process hygiene criterion for *Campylobacter* in broiler carcases would provide one of the best balances between reduction of human campylobacteriosis cases attributed to broiler meat and the economic consequences of the application of such criterion (EC Europe 2012). A step-by-step approach would also be recommendable, making the process hygiene criteria gradually stricter over time.

Campylobacter in Poultry – The Future

Given that *Campylobacter* is a part of the normal gut flora of birds (and is a highly successful colonizer of that site), the increasing consumer demand worldwide for low cost chicken meat (while expecting higher animal welfare during production) and the steady reduction in human populations with acquired immunity (either due to lack of natural exposure or to increased susceptibility through age, disease or medication), campylobacteriosis will remain a major foodborne pathogen in most countries (Newell et al. 2010). At the moment, the reliable production of *Campylobacter*-negative flocks, through best-practice biosecurity alone, seems unlikely. In the future, effective vaccines and/or other complementary measures should be achievable outcomes of current research. Although, such measures may not totally eliminate colonization, significant reductions in colonization levels may be feasible. In this case, risk assessment studies show that a significant reduction in public health risk can still be achieved (Nauta and Havelaar 2008). Once chicken is no longer a major source of *Campylobacter*, the importance of other animal reservoirs and transmission routes can be identified and tackled.

Acknowledgments This study was supported by the Netherlands' Organization for Health Research and Development (ZonMw) with grant number 50-52200-98-316 (project name: "DEPiCT – Discerning Environmental Pathways of Campylobacter Transmission").

References

Adnan M, Gao X, Bai X et al (2020) Potential early identification of a large *Campylobacter* outbreak using alternative surveillance data sources: autoregressive modelling and spatiotemporal clustering. JMIR Public Health Surveill 6. https://doi.org/10.2196/18281

Alders RG, Dumas SE, Rukambile E et al (2018) Family poultry: multiple roles, systems, challenges, and options for sustainable contributions to household nutrition security through a planetary health lens. Matern Child Nutr 14(Suppl 3). https://doi.org/10.1111/MCN.12668

Amour C, Gratz J, Mduma ER et al (2016) Epidemiology and impact of *Campylobacter* infection in children in 8 low-resource settings: results from the MAL-ED study. Clin Infect Dis 63:1171–1179. https://doi.org/10.1093/CID/CIW542

Ang CW, Teunis PFM, Herbrink P et al (2011) Seroepidemiological studies indicate frequent and repeated exposure to *Campylobacter* spp. during childhood. Epidemiol Infect 139:1361–1368. https://doi.org/10.1017/S0950268810002359

Arning N, Sheppard SK, Bayliss S et al (2021) Machine learning to predict the source of campylobacteriosis using whole genome data. PLoS Genet 17. https://doi.org/10.1371/JOURNAL.PGEN.1009436

Arshad F, Zahoor T (2019) Assessing the microbiological safety status of most commonly consumed food items sold at local and branded restaurants of Faisalabad, Pakistan. J Food Saf 39: e12587. https://doi.org/10.1111/JFS.12587

Bahrndorff S, Rangstrup-Christensen L, Nordentoft S, Hald B (2013) Foodborne disease prevention and broiler chickens with reduced *Campylobacter* infection. Emerg Infect Dis 19:425. https://doi.org/10.3201/EID1903.111593

Bai Y, Lin XH, Zhu JH et al (2021) Quantification of cross-contamination of *Campylobacter jejuni* during food preparation in a model kitchen in China. J Food Prot 84:850–856. https://doi.org/10.4315/JFP-20-280

Baker MG, Kvalsvig A, Zhang J et al (2012) Declining Guillain-Barré syndrome after campylobacteriosis control, New Zealand, 1988–2010. Emerg Infect Dis 18:226–233. https://doi.org/10.3201/EID1802.111126

Begum S, Sekar M, Gunaseelan L et al (2015) Molecular identification of *Campylobacter jejuni* and *coli* from chicken, calves and dogs to determine its potential threat on human being. Vet World 8:1420–1423. https://doi.org/10.14202/VETWORLD.2015.1420-1423

Berumen A, Lennon R, Breen-Lyles M et al (2021) Characteristics and risk factors of post-infection irritable bowel syndrome after *Campylobacter* enteritis. Clin Gastroenterol Hepatol 19:1855. https://doi.org/10.1016/J.CGH.2020.07.033

Bodhidatta L, Srijan A, Serichantalergs O et al (2013) Bacterial pathogens isolated from raw meat and poultry compared with pathogens isolated from children in the same area of rural Thailand. Southeast Asian J Trop Med Public Health 44(2):259–272. PMID: 23691636

Bull SA, Allen VM, Domingue G et al (2006) Sources of *Campylobacter* spp. colonizing housed broiler flocks during rearing. Appl Environ Microbiol 72:645–652. https://doi.org/10.1128/AEM.72.1.645-652.2006

Burch D (2005) Avian vibrionic hepatitis in laying hens. Vet Rec 157:528. https://doi.org/10.1136/VR.157.17.528-A

Callicott KA, Friorik sdóttir V, Reiersen J et al (2006) Lack of evidence for vertical transmission of *Campylobacter* spp. in chickens. Appl Environ Microbiol 72:5794. https://doi.org/10.1128/AEM.02991-05

Cawthraw SA, Newell DG (2010) Investigation of the presence and protective effects of maternal antibodies against *Campylobacter jejuni* in chickens. Avian Dis 54:86–93. https://doi.org/10.1637/9004-072709-REG.1

Cawthraw SA, Wassenaar TM, Ayling R, Newell DG (1996) Increased colonization potential of *Campylobacter jejuni* strain 81116 after passage through chickens and its implication on the rate of transmission within flocks. Epidemiol Infect 117:213–215. https://doi.org/10.1017/S0950268800001333

CDC (2022a) FoodNet Homepage|CDC. https://www.cdc.gov/foodnet/index.html. Accessed 14 Jan 2023

CDC (2022b) FoodNet Fast|CDC. https://wwwn.cdc.gov/foodnetfast/. Accessed 14 Jan 2023

Cheng AC, Turnidge J, Collignon P et al (2012) Control of fluoroquinolone resistance through successful regulation, Australia. Emerg Infect Dis 18:1453–1460. https://doi.org/10.3201/EID1809.111515

Cody AJ, Bray JE, Jolley KA et al (2017) Core genome multilocus sequence typing scheme for stable, comparative analyses of *Campylobacter jejuni* and *C. coli* human disease isolates. J Clin Microbiol 55:2086–2097. https://doi.org/10.1128/JCM.00080-17

Cody AJ, Maiden MCJ, Strachan NJC, McCarthy ND (2019) A systematic review of source attribution of human campylobacteriosis using multilocus sequence typing. Euro Surveill 24. https://doi.org/10.2807/1560-7917.ES.2019.24.43.1800696

Colles FM, Ali JS, Sheppard SK et al (2011) Campylobacter populations in wild and domesticated Mallard ducks (Anas platyrhynchos). Environ Microbiol Rep 3:574–580. https://doi.org/10.1111/J.1758-2229.2011.00265.X

Cox NA, Richardson LJ, Maurer JJ et al (2012) Evidence for horizontal and vertical transmission in *Campylobacter* passage from hen to her progeny. J Food Prot 75:1896–1902. https://doi.org/10.4315/0362-028.JFP-11-322

Danis K, Di Renzi M, O'Neill W et al (2009) Risk factors for sporadic *Campylobacter* infection: an all-Ireland case-control study. Euro Surveill 14:19123. https://doi.org/10.2807/ESE.14.07.19123-EN/CITE/PLAINTEXT

de Zoete MR, van Putten JPM, Wagenaar JA (2007) Vaccination of chickens against *Campylobacter*. Vaccine 25:5548–5557. https://doi.org/10.1016/J.VACCINE.2006.12.002

Deolalikar A, Desiraju K, Laxminarayan R et al (2021) Infectious diseases in the South-East Asia region. Cent Dis Dyn Econ Policy

Didelot X, Bowden R, Wilson DJ et al (2012) Transforming clinical microbiology with bacterial genome sequencing. Nat Rev Genet 13:601–612. https://doi.org/10.1038/NRG3226

Dingle KE, Colles FM, Wareing DRA et al (2001) Multilocus sequence typing system for *Campylobacter jejuni*. J Clin Microbiol 39:14–23. https://doi.org/10.1128/JCM.39.1.14-23.2001

Djennad A, Lo Iacono G, Sarran C et al (2019) Seasonality and the effects of weather on *Campylobacter* infections. BMC Infect Dis 19. https://doi.org/10.1186/S12879-019-3840-7

Domingues AR, Pires SM, Halasa T, Hald T (2012) Source attribution of human campylobacteriosis using a meta-analysis of case-control studies of sporadic infections. Epidemiol Infect 140:970–981. https://doi.org/10.1017/S0950268811002676

Doorduyn Y, Van Pelt W, Siezen CLE et al (2008) Novel insight in the association between salmonellosis or campylobacteriosis and chronic illness, and the role of host genetics in susceptibility to these diseases. Epidemiol Infect 136:1225–1234. https://doi.org/10.1017/S095026880700996X

Doorduyn Y, Van Den Brandhof WE, Van Duynhoven YTHP et al (2010) Risk factors for indigenous *Campylobacter jejuni* and *Campylobacter coli* infections in The Netherlands: a case-control study. Epidemiol Infect 138:1391–1404. https://doi.org/10.1017/S095026881000052X

Douglas Inglis G, McAllister TA, Larney FJ, Topp E (2010) Prolonged survival of *Campylobacter* species in bovine manure compost. Appl Environ Microbiol 76:1110–1119. https://doi.org/10.1128/AEM.01902-09

EC Europe (2012) Analysis of the costs and benefits of setting certain control measures for reduction of *Campylobacter* in broiler meat at different stages of the food chain Final Report. https://food.ec.europa.eu/system/files/2016-10/biosafety_food-borne-disease_campy_cost-bene-analy.pdf. Accessed 23 Jan 2023

EFSA (2010) Analysis of the baseline survey on the prevalence of *Campylobacter* in broiler batches and of *Campylobacter* and *Salmonella* on broiler carcasses in the EU, 2008 – part A: *Campylobacter* and *Salmonella* prevalence estimates. EFSA J 8. https://doi.org/10.2903/J.EFSA.2010.1503

EFSA (2021) The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2018/2019. EFSA J 19. https://doi.org/10.2903/J.EFSA.2021.6490

EFSA BIOHAZ (2010) Scientific Opinion on Quantification of the risk posed by broiler meat to human campylobacteriosis in the EU. EFSA J 8. https://doi.org/10.2903/J.EFSA.2010.1437

EFSA BIOHAZ (2011) Scientific Opinion on *Campylobacter* in broiler meat production: control options and performance objectives and/or targets at different stages of the food chain. EFSA J 9. https://doi.org/10.2903/J.EFSA.2011.2105

EFSA, ECDC (2021) The European Union one health 2020 Zoonoses report. EFSA J 19. https://doi.org/10.2903/J.EFSA.2021.6971

Endtz HP, Mouton RP, Van Der Reyden T et al (1990) Fluoroquinolone resistance in *Campylobacter* spp isolated from human stools and poultry products. Lancet (London, England) 335:787. https://doi.org/10.1016/0140-6736(90)90897-E

Franz E, Mughini Gras L, Dallman T (2016) Significance of whole genome sequencing for surveillance, source attribution and microbial risk assessment of foodborne pathogens. Curr Opin Food Sci 8:74–79. https://doi.org/10.1016/J.COFS.2016.04.004

Fravalo P, Kooh P, Mughini-Gras L et al (2021) Risk factors for sporadic campylobacteriosis: a systematic review and meta-analysis. Microb Risk Anal 17:100118. https://doi.org/10.1016/J.MRAN.2020.100118

French N, Barrigas M, Brown P et al (2005) Spatial epidemiology and natural population structure of *Campylobacter jejuni* colonizing a farmland ecosystem. Environ Microbiol 7:1116–1126. https://doi.org/10.1111/J.1462-2920.2005.00782.X

Friedman CR, Hoekstra RM, Samuel M et al (2004) Risk factors for sporadic *Campylobacter* infection in the United States: a case-control study in FoodNet sites. Clin Infect Dis 38(Suppl 3). https://doi.org/10.1086/381598

Friesema IHM, Havelaar AH, Westra PP et al (2012) Poultry culling and campylobacteriosis reduction among humans, The Netherlands. Emerg Infect Dis 18:466–468. https://doi.org/10.3201/EID1803.111024

Gahamanyi N, Mboera LEG, Matee MI et al (2020) Prevalence, risk factors, and antimicrobial resistance profiles of thermophilic *Campylobacter* species in humans and animals in sub-Saharan Africa: a systematic review. Int J Microbiol. https://doi.org/10.1155/2020/2092478

Georgiev M, Beauvais W, Guitian J (2017) Effect of enhanced biosecurity and selected on-farm factors on *Campylobacter* colonization of chicken broilers. Epidemiol Infect 145:553–567. https://doi.org/10.1017/S095026881600251X

Gilbert M, Conchedda G, Van Boeckel TP et al (2015) Income disparities and the global distribution of intensively farmed chicken and pigs. PLoS One 10. https://doi.org/10.1371/JOURNAL.PONE.0133381

Gillespie IA, O'Brien SJ, Frost JA et al (2002) A case-case comparison of *Campylobacter coli* and *Campylobacter jejuni* infection: a tool for generating hypotheses. Emerg Infect Dis 8:937–942. https://doi.org/10.3201/eid0809.010817

Gilpin BJ, Walker T, Paine S et al (2020) A large scale waterborne Campylobacteriosis outbreak, Havelock North, New Zealand. J Infect 81:390–395. https://doi.org/10.1016/J.JINF.2020.06.065

Guyard-Nicodème M, Keita A, Quesne S et al (2016) Efficacy of feed additives against *Campylobacter* in live broilers during the entire rearing period. Poult Sci 95:298–305. https://doi.org/10.3382/PS/PEV303

Haagsma JA, Siersema PD, De Wit NJ, Havelaar AH (2010) Disease burden of post-infectious irritable bowel syndrome in The Netherlands. Epidemiol Infect 138:1650–1656. https://doi.org/10.1017/S0950268810000531

Harrison L, Mukherjee S, Hsu CH et al (2021) Core genome MLST for source attribution of *Campylobacter coli*. Front Microbiol 12. https://doi.org/10.3389/FMICB.2021.703890

Havelaar AH, Swart A (2016) Impact of waning acquired immunity and asymptomatic infections on case-control studies for enteric pathogens. Epidemics 17:56–63. https://doi.org/10.1016/J.EPIDEM.2016.11.004

Havelaar AH, Mangen MJJ, De Koeijer AA et al (2007) Effectiveness and efficiency of controlling *Campylobacter* on broiler chicken meat. Risk Anal 27:831–844. https://doi.org/10.1111/J.1539-6924.2007.00926.X

Havelaar AH, Van Pelt W, Ang CW et al (2009) Immunity to *Campylobacter*: its role in risk assessment and epidemiology. Crit Rev Microbiol 35:1–22. https://doi.org/10.1080/10408410802636017

Havelaar AH, Haagsma JA, Mangen MJJ et al (2012) Disease burden of foodborne pathogens in The Netherlands, 2009. Int J Food Microbiol 156:231–238. https://doi.org/10.1016/J.IJFOODMICRO.2012.03.029

Havelaar AH, Ivarsson S, Löfdahl M, Nauta MJ (2013) Estimating the true incidence of campylobacteriosis and salmonellosis in the European Union, 2009. Epidemiol Infect 141: 293–302. https://doi.org/10.1017/S0950268812000568

Havelaar AH, Kirk MD, Torgerson PR et al (2015) World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. PLoS Med 12. https://doi.org/10.1371/JOURNAL.PMED.1001923

Helms M, Simonsen J, Mølbak K (2006) Foodborne bacterial infection and hospitalization: a registry-based study. Clin Infect Dis 42:498–506. https://doi.org/10.1086/499813

Hepworth PJ, Ashelford KE, Hinds J et al (2011) Genomic variations define divergence of water/wildlife-associated *Campylobacter jejuni* niche specialists from common clonal complexes. Environ Microbiol 13:1549–1560. https://doi.org/10.1111/J.1462-2920.2011.02461.X

Hermans D, Martel A, Garmyn A et al (2012) Application of medium-chain fatty acids in drinking water increases *Campylobacter jejuni* colonization threshold in broiler chicks. Poult Sci 91: 1733–1738. https://doi.org/10.3382/PS.2011-02106

Hoffmann S, Batz MB, Morris JG (2012) Annual cost of illness and quality-adjusted life year losses in the United States due to 14 foodborne pathogens. J Food Prot 75:1292–1302. https://doi.org/10.4315/0362-028X.JFP-11-417

Hsu CH, Harrison L, Mukherjee S et al (2020) Core genome multilocus sequence typing for food animal source attribution of human *Campylobacter jejuni* infections. Pathogens (Basel, Switzerland) 9:1–12. https://doi.org/10.3390/PATHOGENS9070532

Jansen W, Reich F, Klein G (2014) Large-scale feasibility of organic acids as a permanent preharvest intervention in drinking water of broilers and their effect on foodborne *Campylobacter* spp. before processing. J Appl Microbiol 116:1676–1687. https://doi.org/10.1111/JAM.12490

Jore S, Viljugrein H, Brun E et al (2010) Trends in *Campylobacter* incidence in broilers and humans in six European countries, 1997–2007. Prev Vet Med 93:33–41. https://doi.org/10.1016/J.PREVETMED.2009.09.015

Kalupahana RS, Kottawatta KSA, Kanankege KST et al (2013) Colonization of *Campylobacter* spp. in broiler chickens and laying hens reared in tropical climates with low-biosecurity housing. Appl Environ Microbiol 79:393–395. https://doi.org/10.1128/AEM.02269-12

Kalupahana RS, Mughini-Gras L, Kottawatta SA et al (2018) Weather correlates of *Campylobacter* prevalence in broilers at slaughter under tropical conditions in Sri Lanka. Epidemiol Infect 146: 972–979. https://doi.org/10.1017/S0950268818000894

Knipper AD, Ghoreishi N, Crease T (2022) Prevalence and concentration of *Campylobacter* in faeces of dairy cows: a systematic review and meta-analysis. PLoS One 17. https://doi.org/10.1371/JOURNAL.PONE.0276018

Kotloff KL, Nataro JP, Blackwelder WC et al (2013) Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet (London, England) 382:209–222. https://doi.org/10.1016/S0140-6736(13)60844-2

Kottawatta KSA, Van Bergen MAP, Abeynayake P et al (2017) *Campylobacter* in broiler chicken and broiler meat in Sri Lanka: influence of semi-automated vs. wet market processing on *Campylobacter* contamination of broiler neck skin samples. Foods 6. https://doi.org/10.3390/FOODS6120105

Koutsoumanis K, Allende A, Alvarez-Ordóñez A et al (2020) Update and review of control options for *Campylobacter* in broilers at primary production. EFSA J Eur Food Saf Auth 18:1–89. https://doi.org/10.2903/J.EFSA.2020.6090

Kuhn KG, Nielsen EM, Mølbak K, Ethelberg S (2018) Determinants of sporadic *Campylobacter* infections in Denmark: a nationwide case-control study among children and young adults. Clin Epidemiol 10:1695–1707. https://doi.org/10.2147/CLEP.S177141

Kulasooriya GDBN, Amarasiri MKUT, Abeykoon AMH, Kalupahana RS (2019) *Salmonella*, *Campylobacter* and *Escherichia coli* in raw chicken meat, chicken products and cooked chicken

in retail markets in Kandy, Sri Lanka. Sri Lanka Vet J 66:19. https://doi.org/10.4038/SLVJ.V66I1.33

Lagerweij G, Pijnacker R, Frieseman I et al (2020) Disease burden of food-related pathogensin the Netherlands, 2019. RIVM Briefrapport 0117

Lake RJ, Campbell DM, Hathaway SC et al (2021) Source attributed case-control study of campylobacteriosis in New Zealand. Int J Infect Dis 103:268–277. https://doi.org/10.1016/J.IJID.2020.11.167

Liu J, Platts-Mills JA, Juma J et al (2016) Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. Lancet (London, England) 388:1291–1301. https://doi.org/10.1016/S0140-6736(16)31529-X

Llarena AK, Skjerve E, Bjørkøy S et al (2022) Rapid detection of *Campylobacter* spp. in chickens before slaughter. Food Microbiol 103. https://doi.org/10.1016/J.FM.2021.103949

Lu T, Marmion M, Ferone M et al (2020) On farm interventions to minimise *Campylobacter* spp. contamination in chicken. Br Poult Sci 62:53–67. https://doi.org/10.1080/00071668.2020.1813253. https://doi-org.proxy.library.uu.nl/101080/0007166820201813253

MacDonald E, White R, Mexia R et al (2015) Risk factors for sporadic domestically acquired *Campylobacter* infections in Norway 2010–2011: a national prospective case-control study. PLoS One 10. https://doi.org/10.1371/JOURNAL.PONE.0139636

Man SM (2011) The clinical importance of emerging *Campylobacter* species. Nat Rev Gastroenterol Hepatol 8:669–685. https://doi.org/10.1038/NRGASTRO.2011.191

Marks SL, Rankin SC, Byrne BA, Weese JS (2011) Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. J Vet Intern Med 25:1195–1208. https://doi.org/10.1111/J.1939-1676.2011.00821.X

Monge S, Teunis P, Friesema I et al (2018) Immune response-eliciting exposure to *Campylobacter* vastly exceeds the incidence of clinically overt campylobacteriosis but is associated with similar risk factors: a nationwide serosurvey in The Netherlands. J Infect 77:171–177. https://doi.org/10.1016/J.JINF.2018.04.016

Mossong J, Mughini-Gras L, Penny C et al (2016) Human campylobacteriosis in Luxembourg, 2010–2013: a case-control study combined with multilocus sequence typing for source attribution and risk factor analysis. Sci Rep 6(1):1–12. https://doi.org/10.1038/SREP20939

Mota-Gutierrez J, Lis L, Lasagabaster A et al (2022) *Campylobacter* spp. prevalence and mitigation strategies in the broiler production chain. Food Microbiol 104. https://doi.org/10.1016/J.FM.2022.103998

Mourkas E, Taylor AJ, Méric G et al (2020) Agricultural intensification and the evolution of host specialism in the enteric pathogen *Campylobacter jejuni*. Proc Natl Acad Sci 117:11018–11028. https://doi.org/10.6084/m9.figshare.9929054

Mughini Gras L, Smid JH, Wagenaar JA et al (2012) Risk factors for campylobacteriosis of chicken, ruminant, and environmental origin: a combined case-control and source attribution analysis. PLoS One 7. https://doi.org/10.1371/JOURNAL.PONE.0042599

Mughini Gras L, Smid JH, Wagenaar JA et al (2013) Increased risk for *Campylobacter jejuni* and *C. coli* infection of pet origin in dog owners and evidence for genetic association between strains causing infection in humans and their pets. Epidemiol Infect 141:2526–2535. https://doi.org/10.1017/S0950268813000356

Mughini Gras L, Smid JH, Wagenaar JA et al (2014) Campylobacteriosis in returning travellers and potential secondary transmission of exotic strains. Epidemiol Infect 142:1277–1288. https://doi.org/10.1017/S0950268813002069

Mughini Gras L, Penny C, Ragimbeau C et al (2016) Quantifying potential sources of surface water contamination with *Campylobacter jejuni* and *Campylobacter coli*. Water Res 101:36–45. https://doi.org/10.1016/J.WATRES.2016.05.069

Mughini Gras L, Chanamé Pinedo L, Pijnacker R et al (2021a) Impact of the COVID-19 pandemic on human salmonellosis in The Netherlands. Epidemiol Infect 149:e254. https://doi.org/10.1017/S0950268821002557

Mughini Gras L, Pijnacker R, Coipan C et al (2021b) Sources and transmission routes of campylobacteriosis: a combined analysis of genome and exposure data. J Infect 82:216–226. https://doi.org/10.1016/J.JINF.2020.09.039

Mulder A, Franz E, de Rijk S et al (2020) Tracing the animal sources of surface water contamination with *Campylobacter jejuni* and *Campylobacter coli*. Water Res 187:116421. https://doi.org/10.1016/J.WATRES.2020.116421

Müllner P, Collins-Emerson JM, Midwinter AC et al (2010) Molecular epidemiology of *Campylobacter jejuni* in a geographically isolated country with a uniquely structured poultry industry. Appl Environ Microbiol 76:2145–2154. https://doi.org/10.1128/AEM.00862-09

Murphy C, Carroll C, Jordan KN (2006) Environmental survival mechanisms of the foodborne pathogen *Campylobacter jejuni*. J Appl Microbiol 100:623–632. https://doi.org/10.1111/J.1365-2672.2006.02903.X

Nauta MJ, Havelaar AH (2008) Risk-based standards for *Campylobacter* in the broiler meat chain. Food Control 19:372–381. https://doi.org/10.1016/J.FOODCONT.2007.04.016

Newell DG, Shreeve JE, Toszeghy M et al (2001) Changes in the carriage of *Campylobacter* strains by poultry carcasses during processing in abattoirs. Appl Environ Microbiol 67:2636–2640. https://doi.org/10.1128/AEM.67.6.2636-2640.2001

Newell DG, Koopmans M, Verhoef L et al (2010) Food-borne diseases – the challenges of 20 years ago still persist while new ones continue to emerge. Int J Food Microbiol 139(Suppl 1). https://doi.org/10.1016/J.IJFOODMICRO.2010.01.021

Newell DG, Elvers KT, Dopfer D et al (2011) Biosecurity-based interventions and strategies to reduce *Campylobacter* spp. on poultry farms. Appl Environ Microbiol 77:8605–8614. https://doi.org/10.1128/AEM.01090-10

Nhung NT, Cuong NV, Thwaites G, Carrique-Mas J (2016) Antimicrobial usage and antimicrobial resistance in animal production in Southeast Asia: a review. Antibiotics (Basel, Switzerland) 5. https://doi.org/10.3390/ANTIBIOTICS5040037

Nicholson FA, Groves SJ, Chambers BJ (2005) Pathogen survival during livestock manure storage and following land application. Bioresour Technol 96:135–143. https://doi.org/10.1016/j.biortech.2004.02.030

Nothaft H, Perez-Muñoz ME, Yang T et al (2021) Improving chicken responses to glycoconjugate vaccination against *Campylobacter jejuni*. Front Microbiol 12. https://doi.org/10.3389/FMICB.2021.734526

Olson EG, Micciche AC, Rothrock MJ et al (2021) Application of bacteriophages to limit *Campylobacter* in poultry production. Front Microbiol 12. https://doi.org/10.3389/FMICB.2021.458721

Papri N, Islam Z, Leonhard SE et al (2021) Guillain-Barré syndrome in low-income and middle-income countries: challenges and prospects. Nat Rev Neurol 17:285–296. https://doi.org/10.1038/S41582-021-00467-Y

Pérez-Reche FJ, Rotariu O, Lopes BS et al (2020) Mining whole genome sequence data to efficiently attribute individuals to source populations. Sci Rep 10. https://doi.org/10.1038/S41598-020-68740-6

Pires SM, Evers EG, Van Pelt W et al (2009) Attributing the human disease burden of foodborne infections to specific sources. Foodborne Pathog Dis 6:417–424. https://doi.org/10.1089/FPD.2008.0208

Pires SM, Vigre H, Makela P, Hald T (2010) Using outbreak data for source attribution of human salmonellosis and campylobacteriosis in Europe. Foodborne Pathog Dis 7:1351–1361. https://doi.org/10.1089/FPD.2010.0564

Platts-Mills JA, Babji S, Bodhidatta L et al (2015) Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). Lancet Glob Health 3:e564–e575. https://doi.org/10.1016/S2214-109X(15)00151-5

Plishka M, Sargeant JM, Greer AL et al (2021) The prevalence of *Campylobacter* in live cattle, Turkey, chicken, and swine in the United States and Canada: a systematic review and meta-analysis. Foodborne Pathog Dis 18:230–242. https://doi.org/10.1089/FPD.2020.2834

Poulsen MN, Pollak J, Sills DL et al (2018) Residential proximity to high-density poultry operations associated with campylobacteriosis and infectious diarrhea. Int J Hyg Environ Health 221: 323–333. https://doi.org/10.1016/J.IJHEH.2017.12.005

Premarathne JMKJK, Satharasinghe DA, Huat JTY et al (2017) Impact of human *Campylobacter* infections in Southeast Asia: the contribution of the poultry sector. Crit Rev Food Sci Nutr 57: 3971–3986. https://doi.org/10.1080/10408398.2016.1266297

Rogawski ET, Liu J, Platts-Mills JA et al (2018) Use of quantitative molecular diagnostic methods to investigate the effect of enteropathogen infections on linear growth in children in low-resource settings: longitudinal analysis of results from the MAL-ED cohort study. Lancet Glob Health 6:e1319–e1328. https://doi.org/10.1016/S2214-109X(18)30351-6

Rosner BM, Schielke A, Didelot X et al (2017) A combined case-control and molecular source attribution study of human *Campylobacter* infections in Germany, 2011–2014. Sci Rep 7:5139. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5505968/

Sahin O, Terhorst SA, Burrough ER et al (2017) Key role of capsular polysaccharide in the induction of systemic infection and abortion by hypervirulent *Campylobacter jejuni*. Infect Immun 85. https://doi.org/10.1128/IAI.00001-17/ASSET/AD5A3732-BDCA-4BA1-9578-8DCCCDA622E1/ASSETS/GRAPHIC/ZII00617-2051-T01.JPEG

Sales-Ortells H, Agostini G, Medema G (2015) Quantification of waterborne pathogens and associated health risks in urban water. Environ Sci Technol 49:6943–6952. https://doi.org/10.1021/ACS.EST.5B00625

Scallan E, Hoekstra RM, Angulo FJ et al (2011) Foodborne illness acquired in the United States – major pathogens. Emerg Infect Dis 17:7–15. https://doi.org/10.3201/EID1701.P11101

Schneitz C (2005) Competitive exclusion in poultry – 30 years of research. Food Control 16:657–667. https://doi.org/10.1016/J.FOODCONT.2004.06.002

Sears A, Baker MG, Wilson N et al (2011) Marked campylobacteriosis decline after interventions aimed at poultry, New Zealand. Emerg Infect Dis 17:1007–1015. https://doi.org/10.3201/EID/1706.101272

Sibanda N, McKenna A, Richmond A et al (2018) A review of the effect of management practices on *Campylobacter* prevalence in poultry farms. Front Microbiol 9. https://doi.org/10.3389/FMICB.2018.02002

Sopwith W, Birtles A, Matthews M et al (2008) Identification of potential environmentally adapted *Campylobacter jejuni* strain, United Kingdom. Emerg Infect Dis 14:1769–1773. https://doi.org/10.3201/EID1411.071678

Sorgentone S, Busani L, Calistri P et al (2021) A large food-borne outbreak of campylobacteriosis in kindergartens and primary schools in Pescara, Italy, May–June 2018. J Med Microbiol 70. https://doi.org/10.1099/JMM.0.001262

Stern NJ, Hiett KL, Alfredsson GA et al (2003) *Campylobacter* spp. in Icelandic poultry operations and human disease. Epidemiol Infect 130:23–32. https://doi.org/10.1017/S0950268802007914

Stone DM, Chander Y, Bekele AZ et al (2014) Genotypes, antibiotic resistance, and ST-8 genetic clone in *Campylobacter* isolates from sheep and goats in Grenada. Vet Med Int. https://doi.org/10.1155/2014/212864

Suzuki H, Yamamoto S (2009) Campylobacter contamination in retail poultry meats and by-products in the world: a literature survey. J Vet Med Sci 71:255–261. https://doi.org/10.1292/JVMS.71.255

Swift L, Hunter PR (2004) What do negative associations between potential risk factors and illness in analytical epidemiological studies of infectious disease really mean? Eur J Epidemiol 19:219–223. https://doi.org/10.1023/B:EJEP.0000020453.84296.F6

Tam CC, Rodrigues LC, Viviani L et al (2012) Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. Gut 61:69–77. https://doi.org/10.1136/GUT.2011.238386

Tang Y, Meinersmann RJ, Sahin O et al (2017) Wide but variable distribution of a hypervirulent *Campylobacter jejuni* clone in beef and dairy cattle in the United States. Appl Environ Microbiol 83. https://doi.org/10.1128/AEM.01425-17

Teunis PFM, Falkenhorst G, Ang CW et al (2013) Campylobacter seroconversion rates in selected countries in the European Union. Epidemiol Infect 141:2051–2057. https://doi.org/10.1017/S0950268812002774

Tustin J, Laberge K, Michel P et al (2011) A national epidemic of campylobacteriosis in Iceland, lessons learned. Zoonoses Public Health 58:440–447. https://doi.org/10.1111/J.1863-2378.2010.01387.X

van Gerwe T, Bouma A, Klinkenberg D et al (2010) Medium chain fatty acid feed supplementation reduces the probability of *Campylobacter jejuni* colonization in broilers. Vet Microbiol 143:314–318. https://doi.org/10.1016/J.VETMIC.2009.11.029

Vandeplas S, Dubois-Dauphin R, Palm R et al (2010) Prevalence and sources of *Campylobacter* spp. contamination in free-range broiler production in the southern part of Belgium. Biotechnol Agron Soc Environ 14:279–288

Vellinga A, Van Loock F (2002) The dioxin crisis as experiment to determine poultry-related *Campylobacter* enteritis. Emerg Infect Dis 8:19–22

Wagenaar JA, Bergen MAPV, Mueller MA et al (2005) Phage therapy reduces *Campylobacter jejuni* colonization in broilers. Vet Microbiol 109:275–283. https://doi.org/10.1016/J.VETMIC.2005.06.002

Wagenaar JA, Mevius DJ, Havelaar AH (2006) Campylobacter in primary animal production and control strategies to reduce the burden of human campylobacteriosis. Rev Sci Tech Off Int Epiz 25:581–594

Wagenaar JA, French NP, Havelaar AH (2013) Preventing campylobacter at the source: why is it so difficult? Clin Infect Dis 57:1600–1606. https://doi.org/10.1093/cid/cit555

Wagenaar JA, Van Bergen MAP, Blaser MJ et al (2014) *Campylobacter* fetus infections in humans: exposure and disease. Clin Infect Dis 58:1579–1586. https://doi.org/10.1093/cid/ciu085

Walson JL, Pavlinac PB (2018) Targeting enteric pathogens to improve childhood survival and growth. Lancet Glob Health 6:e1258–e1259. https://doi.org/10.1016/S2214-109X(18)30453-4

Wang L, Basuno E, Nguyen T et al (2015) An ecohealth assessment of poultry production clusters (PPCs) for the livelihood and biosecurity improvement of small poultry producers in Asia. Infect Dis Poverty 4. https://doi.org/10.1186/2049-9957-4-6

Wassenaar TM, Newell DG (2000) Genotyping of *Campylobacter* spp. Appl Environ Microbiol 66:1–9. https://doi.org/10.1128/AEM.66.1.1-9.2000

WHO (2017) Strategic action plan to reduce the double burden of in the. WHO

Wu Z, Sippy R, Sahin O et al (2014) Genetic diversity and antimicrobial susceptibility of *Campylobacter jejuni* isolates associated with sheep abortion in the United States and Great Britain. J Clin Microbiol 52:1853–1861. https://doi.org/10.1128/JCM.00355-14

Wu Z, Periaswamy B, Sahin O et al (2016) Point mutations in the major outer membrane protein drive hypervirulence of a rapidly expanding clone of *Campylobacter jejuni*. Proc Natl Acad Sci U S A 113:10690–10695. https://doi.org/10.1073/PNAS.1605869113/-/DCSUPPLEMENTAL

Wu Z, Yaeger MJ, Sahin O et al (2020) A homologous bacterin protects sheep against abortion induced by a hypervirulent *Campylobacter jejuni* clone. Vaccines 8:662. https://doi.org/10.3390/VACCINES8040662

Yaeger M, Mochel JP, Wu Z et al (2021a) Pharmacokinetics of tulathromycin in pregnant ewes (Ovis aries) challenged with *Campylobacter jejuni*. PLoS One 16:e0256862. https://doi.org/10.1371/JOURNAL.PONE.0256862

Yaeger MJ, Sahin O, Plummer PJ et al (2021b) The pathology of natural and experimentally induced *Campylobacter jejuni* abortion in sheep. J Vet Diagn Investig 33:1096. https://doi.org/10.1177/10406387211033293