Chapter 6
Campylobacter: Animal Reservoirs, Human Infections, and Options for Control

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

Abstract Campylobacteriosis is a frequently diagnosed disease in humans. Most infections are considered food-borne and are caused by *Campylobacter jejuni* and *C. coli*. The animal reservoirs of these *Campylobacter,* and the sources and routes of transmission, are described and discussed. Most warm-blooded animals can be colonized by *Campylobacter,* but avians, 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. 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

J. A. Wagenaar (✉) · L. Mughini-Gras
Faculty of Veterinary Medicine, Department of Infectious Diseases and Immunology, Utrecht University, Utrecht, The Netherlands
e-mail: j.wagenaar@uu.nl

J. A. Wagenaar
Central Veterinary Institute of Wageningen UR, Lelystad, The Netherlands

WHO Collaborating Center for Campylobacter/OIE Reference Laboratory for Campylobacteriosis, Lelystad, The Netherlands

D. G. Newell
Food-borne Zoonoses Consultancy, Silver Birches, Wherwell, Andover, UK

R. S. Kalupahana
Faculty of Veterinary Medicine and Animal Science, Department of Veterinary Public Health and Pharmacology, University of Peradeniya, Peradeniya, Sri Lanka

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

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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, bacteriophages, 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.

6.1 Campylobacteriosis: The Disease and Its Burden in Humans

Human campylobacteriosis is primarily caused by *Campylobacter jejuni* and to a much lesser extent by its close relative *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). As these non-*C. jejuni*/*coli* infections represent only a small fraction of all human *Campylobacter* infections, this chapter will focus on *C. jejuni* and *C. coli*, and hereafter *Campylobacter* refers to these two species only. Similarly, hereafter campylobacteriosis refers to the human disease caused by *C. jejuni* and *C. coli*.

Campylobacter is the most commonly reported cause of bacterial infectious intestinal disease (IID). However, systematic disease surveillance programmes, which include campylobacteriosis, are largely limited to industrialized countries, such as the United States (US) and Member States of the European Union (EU) (EFSA and ECDC 2014; Scallan et al. 2011). To date, data from non-industrialized countries are scarce and fragmented, but suggest that campylobacteriosis generally has a lower incidence. 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 under-reporting 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 US in 2011 (Scallan et al. 2011). Nevertheless, serological evidence suggests that exposure to this pathogen, leading to asymptomatic infection, is substantially more frequent (Teunis et al. 2013), such that most individuals have been exposed to the organism by 20 years of age (Ang et al. 2011). 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. There are also differences in disease incidence with age, with peaks in children under 2 years of age and in young adults, and between rural and urban areas, especially in children. Also, interestingly, there is some evidence that the incidence of disease in individuals in later life is increasing.

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 1 in 4 cases in the Netherlands and 1 in 7 cases in the United Kingdom (UK) visit a general practitioner and approximately 1 % of these individuals are hospitalized (Havelaar et al. 2012; Tam et al. 2012). In the acute phase, campylobacteriosis is primarily characterized by gastrointestinal symptoms, such as watery (sometimes bloody) diarrhoea, 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 diarrhoea or systemic infection). However, *Campylobacter* infection can also have serious sequelae, including Guillain-Barré and Miller-Fisher syndromes, reactive arthritis and functional gastrointestinal disorders (Doorduyn et al. 2008; Haagsma et al. 2010; Helms et al. 2006).

Recently the burden of campylobacteriosis has been quantified in term 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 2060 DALYs per year in the Netherlands, calculated for the period 2005–2007. Sequelae accounted for 82 % of this burden (Mangen et al. 2013). In 2009, the DALY estimate increased by approximately 37 % to 3250 DALYs, mainly due to the higher disease incidence (Havelaar et al. 2012). Among foodborne pathogens investigated in the Netherlands, this DALY estimate was second only to *Toxoplasma gondii*. Similar studies in the US 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 programmes implemented, with the exception of Iceland and New Zealand where very specific conditions prevailed (Sears et al. 2011; Stern et al. 2003). 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 more recent years (CDC 2012; EFSA and ECDC 2014). The reasons for this lack of intervention 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.

6.2 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). These bacteria were first described in 1886 by Dr. Theodor Escherich in infants, who died of "cholera infantum". The pathogen was referred to as "Vibrio like organisms" until 1963, when Sebald and Véron (1963) named the genus as *Campylobacter*. Because of their fastidious nature, which causes difficulty in recovery and culture, these bacteria were subsequently neglected by the scientific community. However, in 1972 the first isolation from human faeces was reported (Dekeyser et al. 1972). This finding was an early "One Health" achievement, with Dr. Dekeyser as a veterinarian and Dr. Butzler as a medical doctor noticing the same morphological type of bacteria in chicken and human faeces. This report was quickly followed by improved isolation techniques and the recognition of *Campylobacter* as common agents of acute enteritis in humans (Skirrow 1977).

To date, the genus *Campylobacter* includes 24 species (www.bacterio.cict.fr/c/campylobacter.html) 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 faecal material.

Campylobacter readily generate resistance against an increasing number of classes of antimicrobials. Although antimicrobials are infrequently prescribed for campylobacteriosis, such resistance can have clinical consequences. For example, resistance to fluoroquinolones and tetracyclines is high in many regions of the world, but resistance to erythromycin and gentamicin remains generally low (Ge et al. 2013). Certainly in the UK, travelling abroad is one of the main risk factors for acquiring an infection with a fluoroquinolone-resistant *Campylobacter* strain (CSSSC 2002), suggesting that the indiscriminate use of such antimicrobials in some other countries is significant. 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, ultra-violet radiation, atmospheric oxygen and high salinity. As a consequence *Campylobacter* are unable to grow naturally outside a host and are 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 (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 faecal samples using selective media, containing appropriate antimicrobials, and incubated under reduced oxygen tension, at 42 °C for 72 h. However, the isolation technique and media constituents may vary depending on the matrix under investigation. Interestingly, such variations may affect both the efficacy of recovery and the species and/or strain types recovered (Newell et al. 2001).

The typing of *Campylobacter* has proved extremely challenging. The organisms demonstrate considerable variation at both the phenotypic and genotypic levels and many attempts have been used to exploit this variation to characterize *Campylobacter* for epidemiological studies. Initial typing methods included serotyping and phage typing. However, molecular techniques, such as *fla*-typing, ribotyping, Pulsed Field Gel Electrophoresis (PFGE), Amplified Fragment Length Polymorphism (AFLP) and Random Amplified Polymorphic DNA (RAPD) proved more useful. More recently Multi Locus Sequence Typing (MLST) has become the preferred method for studying the relationships between strains (Dingle et al. 2001). It is now anticipated that whole genome sequencing, with subsequent data processing, will replace MLST (Didelot et al. 2012).

6.3 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. The prevalence of livestock carriage varies with factors like age, husbandry, country, etc. Certainly, a significant proportion of livestock animals is colonized. For example, in a national survey of livestock at slaughter in the UK in 2003 C. *jejuni/C. coli* were isolated from 54.6% of cattle, 43.8% of sheep and 69.3% of pigs (Milnes et al. 2008). Similarly, up to 45% of dogs are colonized (Marks et al. 2011).

The role of *C. jejuni/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 foetuses than *C. fetus*. A recent exception is the spread of a single tetracycline-resistant *C. jejuni* clone causing abortion in sheep throughout the US (Wu et al. 2014), but not yet reported in other countries. Interestingly this clone has also been recovered from diarrhoeic humans in the US, but the route of transmission has not yet been identified. The role of *Campylobacter* as a pathogen in dogs remains debatable (Marks et al. 2011; Burch 2005). 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).

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 body temperature of a bird. Colonization occurs throughout the gut, but primarily in the caecum 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 (Thonart et al. 2010). The organism is highly infectious and in each colonised 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.

6.4 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). It is well recognised 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 (de Jong et al. 2008). 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.

6.4.1 Campylobacter Source Attribution

A general framework for the source attribution of campylobacteriosis has been designed by Nigel French, describing the available information, sources and modelling approaches (Wagenaar et al. 2013a; WHO 2013). Based on this framework,

animals (e.g. cattle, sheep, poultry, pets, wildlife, etc.) are defined as *reservoirs* or *amplifying hosts*; the environment and water sources, the food chain and direct contact with animals are given as examples of *pathways*; drinking water, meat, milk, 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 an hazard in the milk supply (exposure), which manifests itself as an increased risk associated with the consumption of unpasteurized milk (risk factor) (example adapted from Wagenaar et al. 2013a).

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. Specifically, source attribution may be used to prioritize and measure the impact of targeted interventions in the food chain, as well as to identify the most appropriate points at which such interventions should be focussed (Pires et al. 2009) to achieve significant reductions in human exposure (EFSA 2008).

Several approaches can be used for source attribution, including microbiological (microbial subtyping and comparative exposure assessment) and epidemiological (outbreak summary data 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.

6.4.1.1 Source Attribution Based on Outbreak Data

The attribution of sources based on outbreak data is generally considered of limited value for human campylobacteriosis because of the rarity of reported outbreaks (Pires et al. 2010). This is in marked contrast to *Salmonella* infections, which often present as outbreaks (Wagenaar et al. 2013b). *Campylobacter* outbreaks may of course occur more frequently, but are unreported due to the generally intermittent typing of human *Campylobacter* isolates and the lack of internationally accepted harmonized typing methods. Nevertheless, in Europe, campylobacteriosis outbreak data is collected annually and has recently 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 analysed 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. In fact 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).

6.4.1.2 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 for sporadic human campylobacteriosis (Domingues et al. 2012; Doorduyn et al. 2010; Kapperud et al. 2003; Neimann et al. 2003; Stafford et al. 2007; Studahl and Andersson 2000). Other frequently identified risk factors include, the consumption of unpasteurized milk (Friedman et al. 2004; Neimann et al. 2003; Studahl and Andersson 2000), eating in restaurants (Danis et al. 2009; Eberhart-Phillips et al. 1997; Friedman et al. 2004; Gallay et al. 2008), contact with pet dogs (especially puppies) (Carrique-Mas et al. 2005; Doorduyn et al. 2010; Eberhart-Phillips et al. 1997; Friedman et al. 2004; Mughini Gras et al. 2013; Neal and Slack 1997; Stafford et al. 2007; Tenkate and Stafford 2001), contact with livestock (Danis et al. 2009; Eberhart-Phillips et al. 1997; Friedman et al. 2004; Mughini Gras et al. 2012; Potter et al. 2003; Stafford et al. 2007; Studahl and Andersson 2000; Tenkate and Stafford 2001) and foreign travel (Eberhart-Phillips et al. 1997; Friedman et al. 2004; Gallay et al. 2008; Neal and Slack 1997; Neimann et al. 2003; Stafford et al. 2007).

The calculations of the attributable fractions for each risk factor also indicate that, like the outbreak data, chicken consumption accounts for approximately 28% of sporadic cases (Doorduyn et al. 2010). In contrast the contribution of dog ownership to human *Campylobacter* infections is around 4% (Doorduyn et al. 2010). Of course many factors can influence source attribution studies using case-control data. Recently, individuals taking proton-pump inhibitors or having a chronic gastrointestinal disease have been shown to have an increased risk of campylobacteriosis (Doorduyn et al. 2010; Mughini Gras et al. 2012; Neal and Slack 1997; Tam et al. 2009), 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.

Specific immunity against *Campylobacter,* acquired as a result of prior exposure, is another very important confounder of case-control studies. 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), 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).

6.4.1.3 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 development and widespread application of MLST, a genetic technique for investigating bacterial population structures, has recently informed source attribution studies. In its basic form MLST involves the sequencing of seven target housekeeping genes, but additional gene sequences, such as the *fla* gene, are often added. Analysis of the sequences produces a sequence pattern, based on allelic differences, for each strain. This pattern is then assigned to a sequence type (ST). Similar STs, sharing the same alleles at different loci, are considered to be evolutionarily related (i.e. share a common ancestor). Such STs are combined into clonal complexes (Dingle et al. 2001). Early studies of the evolutionary relationships within populations reported that some STs are preferentially associated with certain hosts, such as cattle or poultry. Thus, using complex statistical methods, the probable source attributions can be estimated by comparison of the distribution of STs recovered from diseased humans with those recovered from a range of animal, food and environmental sources (McCarthy et al. 2007; Mughini Gras et al. 2012; Mullner et al. 2009; Wilson et al. 2008; Sheppard et al. 2009; Smid et al. 2013; Strachan et al. 2009).

These MLST studies have provided the most convincing source attribution evidence, for campylobacteriosis, to date. Overall the data estimates that the majority (50–80%) of strains infecting humans come from the chicken reservoir, 20–30% from cattle, and the remainder from other reservoirs (sheep, pigs, and wild animals) (EFSA BIOHAZ 2010).

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

6.4.1.4 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 nation-wide withdrawal of broiler meat from the market, which was concomitant with a 40% decrease in campylobacteriosis, country-wide (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 consumption poultry meat (EFSA BIOHAZ 2010; Friesema et al. 2012). As yet, the transmission routes of such alternative pathways are unclear.

Recently there have been opportunities to study the outcomes of interventions targeted at the poultry production sector and/or to the poultry meat consumer, which 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).

6.4.1.5 Summary of Sources and Transmission Routes

Overall, the conclusion from the source attribution studies described above indicates that chickens are a major reservoir of those *Campylobacter* infecting humans. The importance of broilers as a source of infection is a reflection of the huge numbers of chicken produced and eaten worldwide, the level of colonization of these birds and the production processes involved. As a consequence, most public health effort to reduce campylobacteriosis has focussed on the control and prevention of *Campylobacter* in the poultry meat food chain (see Sect. 6.5). Nevertheless, the handling and consumption of chicken meat is only a part of the human exposure risk, and environmental exposure, through routes as yet unknown, is also important. However, all warm-blooded animals can act as host reservoirs of this infection and exposure to pets and livestock, and their products, can also provide a risk of human disease, although to a lesser extent than poultry. The complexity in exposure routes can generate overall confusing data. For example, children aged less than five years, living in urban areas, seem to be largely exposed to *Campylobacter* strains from chicken, while those living in rural areas are largely exposure to strains from cattle (Mughini Gras et al. 2012; Mullner et al. 2010b; Strachan et al. 2009).

Of course specific risk groups may exist, for example dog (and particularly puppy) owners are at increased risk of *Campylobacter* infection and isolation of identical *Campylobacter* strains in humans and their pets occurs significantly more often than expected by chance (Mughini Gras et al. 2013). However, the direction of any transmission route is indeterminable. Moreover, the association may reflect a common source of infection rather than a direct zoonosis.

Foreign travel is often described as a major risk factor (Eberhart-Phillips et al. 1997; Friedman et al. 2004; Gallay et al. 2008; Neal and Slack 1997; Neimann et al. 2003; Stafford et al. 2007). This increased risk is likely to reflect poorer hygiene in the preparation of food as well as the possible presence of "exotic" *Campylobacter* strains to which travellers had not been previously exposed (Havelaar et al. 2009; Mughini Gras et al. 2014). Moreover, such "exotic" strains, introduced by returning

travellers, might subsequently spread in to the domestic population, through limited person-to-person transmission (Mughini Gras et al. 2014).

6.5 *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 (EFSA BIOHAZ 2011). 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 focussed at the 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 poultry, however, has proved to be very difficult.

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 broilers as these provide the highest risk to humans. 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), 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, then it sheds large numbers of bacteria in its faeces (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 (approximately 42 days for intensively-reared birds) (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 and -positive flocks, many risk factors have been identified, which increase the chance of flock positivity (Newell et al. 2011; Newell and Fearnley 2003; Katsma et al. 2007). 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 broilers 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). This strategy is currently being investigated in other countries (http://www.camcon-eu.net/), but 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 (EFSA BIOHAZ 2011). 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 (EFSA BIOHAZ 2011). The challenge is likely to become even greater in the future given consumer-driven concerns for animal welfare leading to an increasing trend towards 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 (EFSA BIOHAZ 2011). Despite several years of research, vaccination against *Campylobacter* is not yet reliably effective (de Zoete et al. 2007). 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, but research to solve key issues in safety, efficacy and sustainability, is still needed (Lin 2009). The use of medium chain fatty acids has been reported to have at least some effect on *Campylobacter* colonization (Hermans et al. 2012; van Gerwe et al. 2010), 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.

6.5.1 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 (EFSA BIOHAZ 2011).

Cross-contamination can be a significant problem associated with the huge through-put of carcasses (circa 13,000 per hour in many processing plants), slaughter line automation and the high concentrations of *Campylobacter* in caecal contents. Any leakage of faecal 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 (EFSA BIOHAZ 2011).

The decontamination of carcasses with chemicals is allowed in the US and currently practised 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 through-put 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 programme 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) view points, such a strategy would be difficult to implement, especially in those countries with high prevalence of *Campylobacter*-positive flocks (Havelaar et al. 2007).

6.6 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 Sect. 4.1.3).

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 (Baker et al. 2012; Mullner et al. 2010a; Sears et al. 2011). Despite this success, New Zealand still has the highest incidence of campylobacteriosis among reporting countries worldwide.

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.

6.7 *Campylobacter* in Poultry—The Future

Given that *Campylobacter* is a part of the normal gut flora of birds (and is a highly successful coloniser 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 (Bouwknegt et al. 2013; Swart et al. 2012). 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* then the importance of other animal reservoirs and transmission routes can be identified and tackled.

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