Preventing *Campylobacter* at the Source: Why Is It So Difficult?

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Campylobacteriosis in humans, caused by *Campylobacter jejuni* and *Campylobacter coli*, is the most common recognized bacterial zoonosis in the European Union and the United States. The acute phase is characterized by gastrointestinal symptoms. The long-term sequelae (Guillain-Barré syndrome, reactive arthritis, and postinfectious irritable bowel syndrome) contribute considerably to the disease burden. Attribution studies identified poultry as the reservoir responsible for up to 80% of the human *Campylobacter* infections. In the European Union, an estimated 30% of the human infections are associated with consumption and preparation of poultry meat. Until now, interventions in the poultry meat production chain have not been effectively introduced except for targeted interventions in Iceland and New Zealand. Intervention measures (eg, biosecurity) have limited effect or are hampered by economic aspects or consumer acceptance. In the future, a multilevel approach should be followed, aiming at reducing the level of contamination of consumer products rather than complete absence of *Campylobacter*.

Keywords. *Campylobacter*; poultry; source attribution; interventions; food safety.

Clinicians frequently encounter *Campylobacter* as a cause of clinical disease. After a clear increase in incidence of *Campylobacter*-induced disease in the 1980s and 1990s, the prevalence in human populations stabilized in the early 21st century, but is slowly increasing again in recent years. In contrast with other foodborne diseases such as salmonellosis, for which control has been effective in at least some geographical areas (eg, Europe), it seems that *Campylobacter* is less readily controlled in sources from which humans are exposed. This paper aims to give an overview of the current knowledge of the sources of human campylobacteriosis, the efforts to intervene in the food chain, and reasons for failure of effective control.

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CAMPYLOBACTER AND FOOD SAFETY: THE PROBLEM IN HUMANS

Campylobacteriosis is the most common recognized bacterial zoonosis in the European Union and United States [1, 2]. The reported cases are only the tip of the iceberg. Campylobacteriosis in humans is mainly caused by *Campylobacter jejuni* and, to a lesser extent, by *Campylobacter coli*. Other *Campylobacter* species (eg, *C. lari*, *C. upsaliensis*, *C. fetus*) are also reported to cause disease in humans, but the reported number of these non-*jejuni*/*coli* infections worldwide is a small fraction of all *Campylobacter* infections. Therefore, this article focuses on *C. jejuni* and *C. coli*, and hereafter *Campylobacter* refers to these 2 species only. We further restricted the scope of the article to commercial farming in the industrialized world as data from developing countries are very scarce. Depending on severity of the infection, campylobacteriosis in the acute phase is characterized by diarrhea with abdominal cramps, nausea, fever, and bloody stools. The disease is usually self-limiting, and antimicrobial treatment is only indicated

in severe cases. In rare cases, *C. jejuni/coli* can cause a bloodstream infection.

In the European Union, 198 252 cases were reported in 2009, but the true incidence was estimated at 9.2 million cases, a multiplier of 46.7 [1]. In the United States, the multiplier was estimated at 30.3, suggesting an annual incidence of 1.3 million cases [2]; in the United Kingdom, the multiplier was 9.3 with an incidence of 570 000 cases. High seroconversion rates indicate that asymptomatic *Campylobacter* infection is a frequent event, occurring approximately once every year in any adult person in The Netherlands. Hence, only a small fraction of infections lead to symptomatic illness [3]. Approximately 1 of 4 symptomatic cases in the Dutch population visit a general practitioner, and 1% are hospitalized [4]. *Campylobacter* infection is also associated with long-term sequelae, including Guillain-Barré syndrome, reactive arthritis, postinfectious irritable bowel syndrome, and possibly inflammatory bowel disease (the epidemiological evidence is disputed [5]). The estimation of the true incidence of campylobacteriosis was recently discussed in a World Health Organization expert consultation [5]. Together, these different disease manifestations resulted in a disease burden of 3250 disability-adjusted life-years (DALYs) in The Netherlands in 2009. Among food-related pathogens, this was second only to *Toxoplasma gondii*. In the United States, campylobacteriosis was estimated to cause a burden of 13 300 quality-adjusted life-years (QALYs), second only to *Salmonella enterica*, and cost of illness of $1.7 billion annually [6]. *Campylobacter* and poultry was the highest ranking food–pathogen combination with 608 231 illnesses, 6091 hospitalizations, 55 deaths, a burden of 9541 QALYs, and cost of illness of $1.3 billion in the United States [7]. (Please note that DALYs and QALYs are technically similar in that they both express health in time [life-years] and give a weight to years lived with a disease. DALYs measure health loss against an idealized healthy life expectancy, and QALYs measure health gain so they express an inverse value.)

CAMPYLOBACTER: MICROBIOLOGICAL ASPECTS AND PREVALENCE IN ANIMALS

The intestines of warm-blooded animals (mammals and birds) are the amplification vessel for *Campylobacter*. Manure from animals may contaminate surface water through runoff from pasture, presenting a risk for humans when consumed as (untreated) drinking water. Furthermore, humans can be exposed to surface water through direct contact (swimming) or indirect contact (consumption of raw products irrigated with surface water).

Campylobacter can be isolated from the feces of healthy food-producing animals (eg, poultry, pigs, cattle, sheep), wild animals (eg, birds), and companion animals (eg, dogs, cats). Prevalence estimates vary from 71% *C. jejuni/C. coli* in broilers [8], 45% *C. jejuni* in dogs [9], 36% *C. jejuni* in beef cattle, and 42% *C. coli* in pigs [10]. Presence of *Campylobacter* in these animals is usually asymptomatic, although in cattle and sheep *C. jejuni* has been reported to cause sporadic abortions. In the United States, a highly pathogenic *C. jejuni* clone is emerging in ruminants, causing abortion in sheep with evidence for transmission to humans [11]. Except for this specific clone, humans are considered to be the only host species that becomes ill after oral ingestion with *Campylobacter*. The pathogenesis of *C. jejuni* disease in humans and the absence of clinical manifestations in most species is still unexplained. The lack of *Campylobacter*-associated disease or mortality in poultry flocks means there is no economic incentive for farmers to invest in prevention of flock contamination.

ATTRIBUTION OF HUMAN CAMPYLOBACTERIOSIS

Human exposure from animal reservoirs is possible via multiple pathways including food (in particular, poultry meat), the environment, and direct animal contact. Due to the complex transmission cycles, it is difficult to present precise estimates of the contribution of different reservoirs and pathways to human disease. Source attribution is a rapidly evolving field that aims to quantify the contribution of different reservoirs, pathways, exposures, and risk factors to the burden of human illness. A schematic diagram of the various components of source attribution and the different approaches used to inform decision making is shown in Figure 1. Estimations of the quantitative contribution from the different sources can support decisions for targeted intervention [12]. In general, 2 main approaches have been used: microbiological approaches and epidemiological approaches.

Microbiological Approaches

Multilocus sequence typing (MLST) has become the dominant method used for typing *Campylobacter*, in particular when used for reservoir and pathway attribution. Particular types of *Campylobacter* occur more frequently in one (animal) reservoir than in others, so similar isolates from human cases are more likely to result from that reservoir than from others. Based on molecular typing in several countries, it is estimated that the majority (50%–80%) of strains infecting humans originate from the chicken reservoir, 20%–30% from cattle, and the remainder from other reservoirs including sheep, pigs, and wild-living animals [13]. The chicken reservoir includes both broiler chickens and laying hens, and pathways are not limited to consumption and preparation of meat but also include environmental transmission and direct animal contact [14].

Epidemiological Approaches

A meta-analysis of case-control studies of sporadic cases suggested that traveling abroad, eating undercooked chicken,

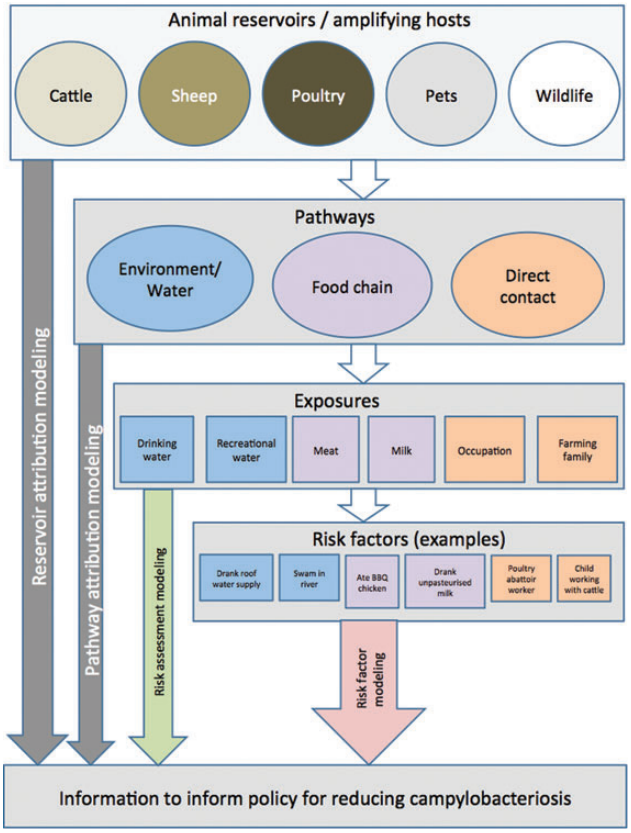

Figure 1. Diagram showing the sources of information and modeling approaches that can be used to inform decision making for the control of campylobacteriosis. The different (animal) reservoirs in which *Campylobacter* species can multiply are illustrated. From these reservoirs, a multitude of vehicles may serve as sources of human exposure, grouped in several categories of transmission pathways. The intensity of exposure is typically dependent on specific risk factors at the individual level. For example, cattle (reservoir) may contaminate the food chain (pathway), resulting in hazard in the milk supply (exposure), which manifests itself as an increased risk associated with the consumption of raw, unpasteurized milk (risk factor). The figure also shows how different methods for source attribution take different stages of the overall transmission diagram into account. As examples, the relative contribution of animal reservoirs to the burden of campylobacteriosis can be estimated using models based on microbial typing of isolates from clinical cases and animals, whereas risk factors can be determined using epidemiologic studies, such as case-control studies. Information on individual risk factors may be used directly to inform control measures, or may be aggregated to provide estimates of the relative contributions of exposures, pathways, and reservoirs.

environmental sources, eating in a restaurant (particularly chicken), and direct contact with farm animals were significant risk factors for human campylobacteriosis [15]. MLST typing data suggested that in The Netherlands, 60%–70% of strains from human infections could be attributed to the chicken reservoir. Reanalyzing data from a case-control study, 42% of the chicken-related strains could be attributed to consumption of broiler meat [16]. Hence, overall approximately 30% of all cases were attributed to consumption of chicken meat, which is similar to other case-control studies in different countries. Combining information on multiple variables to infer the relative contributions of reservoirs, pathways, and exposures should be done with care, due to the complex nature of causal pathways. However, these studies are also valuable in identifying specific, non-food-related risk factors that can be the focus of intervention. For example, in the Dutch study, the largest non-food-related risk factor was the use of proton pump inhibitors (PPIs), explaining 22% of cases overall [16]. Other studies confirm this increased risk for enteric disease, and "the clinical implication of chronic PPI use among hospitalized patients placed on antibiotics and travellers departing for areas with high incidence of diarrhoea should be considered by their physicians" [17].

Comparative risk assessment aims to quantify human exposure by all potential pathways, by combining data on prevalence and numbers of bacteria with data on the intensity of exposure (food consumption, frequency of animal contact, etc). The only comparative exposure assessment for *Campylobacter* published to date suggests that two-thirds of all human exposure is related to direct animal contact [18]. Exposure cannot, however, be directly related to illness, as some exposures are highly clustered and highly exposed individuals may be protected by acquired immunity [19].

Targeted interventions and "natural experiments" can be used to evaluate changes in the incidence of reported campylobacteriosis in situations when there are marked changes in exposure due to national policy interventions or incidents in the food chain. The impact of targeted interventions in Iceland (72% reduction in human incidence) and New Zealand (54% decline in human incidence with a 74% reduction in the number of cases attributed to poultry) suggest an important contribution of chicken meat to human campylobacteriosis [20, 21]. In New Zealand, a concurrent decline in Guillain-Barré syndrome was also observed [22]. In Belgium, reported campylobacteriosis declined by 40% in June 1999, when no broiler meat was available due to feed contamination with dioxins [23]. Finally, in The Netherlands, poultry culling during the avian influenza epidemic in 2003 resulted in a concurrent decrease of campylobacteriosis in the affected area [14]. The decline could not be explained only by reduced consumption of broiler meat, suggesting that laying hens are also reservoirs for human campylobacteriosis by as yet unidentified pathways.

CONTAMINATION OF FOOD OF ANIMAL ORIGIN

The surface of the carcasses can become contaminated during the slaughter process. Intestinal flora, including *Campylobacter*, can be isolated from the surface of the carcasses of poultry, pigs, and cattle after slaughtering [24, 25]. Due to different techniques in processing influencing the dryness of pig and cattle

carcasses [26], *Campylobacter* is less prevalent on pork and beef compared to poultry meat. This may explain why attribution studies identify poultry meat as an important source for human campylobacteriosis. Because the presence of *Campylobacter* in poultry was associated with human disease in the early 1970s [27], considerable efforts have been undertaken to control *Campylobacter*. In contrast to human salmonellosis, eggs have never been associated with human campylobacteriosis.

POULTRY AND *CAMPYLOBACTER* AND PREVENTION OF FLOCK COLONIZATION

Broilers, turkeys, ducks, and all other types of poultry can become colonized with *Campylobacter* [28]. Vertical transmission of *Campylobacter* from parents to progeny through eggs is an extremely rare event, if it happens at all [29, 30], so each broiler cycle starts with a negative flock. If broiler houses are adequately cleaned and disinfected prior to arrival of the new animals, the flocks usually stay free of *Campylobacter* in the first 1–2 weeks. Once introduced into a flock, *Campylobacter* spreads rapidly. Virtually all animals become colonized, shedding up to 10^8 *Campylobacter*/g of cecal contents. These counts remain at a similar level till slaughter (42 days in conventional production systems).

Flock prevalence is highly seasonal with peak occurrence in the summer months overlapping with the peaks in human campylobacteriosis, although the determinants of seasonal patterns in humans and poultry are still unknown [31]. The incidence of *Campylobacter*-positive flocks varies strongly per country. In Europe, the northern countries (Norway, Iceland, Finland, Sweden) have a lower prevalence and shorter summer peaks compared to southern countries, a feature attributed to climate conditions [32].

WHERE TO INTERVENE IN THE FOOD CHAIN MOST EFFICIENTLY?

As broiler meat is the largest identified source of human exposure to *Campylobacter*, food safety authorities and producers are seeking cost-effective ways to intervene in the poultry production chain. Reducing the prevalence of *Campylobacter* colonization in living animals on farms will decrease the introduction of high numbers of *Campylobacter* into the slaughterhouse [33]. This may result in a low concentration or absence of *Campylobacter* on the final product. As controlling *Campylobacter* on-farm would impact transmission not only via meat but also via other (environmental) pathways, this option would potentially have a higher public health impact than interventions later in the chain.

Many studies have been performed to identify risk factors for flocks becoming positive [34]. Colonization of flocks is associated with increased age of the animals, the number of houses on a farm, the presence of other animals on the farm or direct surroundings, a formerly *Campylobacter*-colonized flock in the same house, and partial depopulation (a breach in biosecurity by collecting part of the flock for slaughter to reduce bird density, giving the remaining animals more space to grow). The common theme of many of these risk factors is (lack of) biosecurity.

Theoretically, a high level of biosecurity on farm level should prevent the introduction of *Campylobacter* into a flock [35]. Instruction regarding increased hygiene may reduce the prevalence of *Campylobacter,* as shown in Norway [36]. However, even an extremely high level of biosecurity does not guarantee a *Campylobacter*-free flock at slaughter. *Campylobacter* is ubiquitous around broiler houses, and even if facilities such as anterooms, disinfection for boots, separate clothing, and utensils are available, they must be used consistently in order to prevent flock colonization. Flies can be carriers of Campylobacter, and the fly traffic in and out of broiler houses is huge (>30 000 flies per production cycle [37]). Installation of fly screens around ventilation openings showed delayed and reduced *Campylobacter* colonization in flocks [38].

An overview of potential *Campylobacter* interventions along the poultry meat production chain has been described in an European Food Safety Authority opinion [39]. Despite considerable scientific investments, no vaccine is available that prevents or reduces *Campylobacter* colonization in poultry. The use of competitive exclusion, establishing a stabilized gut flora in young animals, effective in the control of *Salmonella*, has not been effective against *Campylobacter* [40]. Once flocks are colonized, there are no methods commercially available to reduce the number of *Campylobacter* in the cecal contents. In a commercial poultry slaughter line, up to 13 000 animals per hour are processed. The process is completely automated, providing a challenge for hygienic slaughter and carcass preparation. Due to the high concentration of *Campylobacter* in the intestines, chicken carcasses can become contaminated at the surface during processing (eg, after defeathering or rupture of the gut during evisceration). Technical improvement of the slaughtering process to prevent contamination of meat is expected to have an effect in the reduction of *Campylobacter* contamination, but evidence-based interventions are not yet available. Nevertheless, there are considerable differences between the level of end-product contamination in different slaughterhouses [41], suggesting that benchmarking studies may lead to practical guidelines for site-specific interventions. Alternative options are the chemical and physical decontamination of meat, but their effectiveness is typically limited to a reduction of 1–2 log units. In the European Union, chemical decontamination is allowed only for specific, approved compounds. In the United States, several decontaminating agents including organic

acids, quaternary ammonium compounds, acidified sodium chlorite, and trisodium phosphate are being applied in practice. Physical decontamination (eg, ultraviolet light, irradiation) is allowed, but effectiveness is expected to be limited, particularly when implemented in high-volume slaughter lines. Consumer preferences (eg, for fresh, untreated poultry products), acceptance (eg, consumers do not like irradiated products), and economic arguments (higher number of animals per hour reduces costs but puts more stress on care for the individual carcass) prevent implementation of potentially effective interventions. In Iceland, freezing of contaminated poultry meat was introduced in 1999 as an effective intervention measure. There is a 2–3 log reduction of *Campylobacter* counts associated with freezing, and this resulted in a reduction in campylobacteriosis cases. In Iceland, this was feasible because of a relatively low incidence of *Campylobacter* in poultry flocks and a limited volume of meat that had to be frozen. Economic and logistic reasons hamper a broader implementation of this intervention [42].

Even though chicken is rarely eaten raw, the high frequency and level of contamination of fresh meat results in failures of the hygiene barriers during food preparation. We consider undercooking of chicken to be of minor importance as internal contamination of the meat with *Campylobacter* is rare and of low concentration [43]. Cross-contamination in the kitchen from contaminated meat to items that will not be cooked is considered an important pathway [39]. Intensification of consumer education is not expected to resolve this problem, because changing routine cooking behavior requires very specific cues [44]. Reducing the contamination of fresh chicken entering the kitchen is currently the most effective approach and most efficiently realized at slaughter [42].

PUBLIC HEALTH IMPACT OF REDUCING HUMAN EXPOSURE TO *CAMPYLOBACTER*

Natural experiments and interventions applied at a national level as discussed above suggest that reducing human exposure to *Campylobacter* will result in lower disease incidence. This is consistent with all risk assessment studies published thus far [45]. Unlike many other bacteria, *Campylobacter* is unable to multiply outside the intestines of warm-blooded animals. This implies that when carcasses leave the slaughterhouse, bacteria will die and/or be removed from products and only a small fraction of bacteria initially present on the meat will ultimately reach the consumer. Hence, a zero-tolerance approach for *Campylobacter* on fresh chicken meat is not necessary to achieve a high degree of consumer protection. Several risk assessment studies have demonstrated that consumer risks are mainly associated with highly contaminated products and that preventing these from reaching the consumer is both effective and efficient [39, 46]. In New Zealand, the number of campylobacteriosis notifications increased markedly between 2000 and 2007. To examine the possible link between human cases and poultry, a sentinel surveillance site was established in 2005 to study the molecular epidemiology of *C. jejuni* using MLST. Studies showed that 60%–81% of retail poultry carcasses from the major suppliers were contaminated with *C. jejuni*. Differences were detected in the probability and level of contamination and the relative frequency of genotypes for individual poultry suppliers and humans, and there was evidence of both ubiquitous and supplier-associated strains, an epidemiological pattern not recognized yet in other countries. The common poultry sequence types were also common in human clinical cases, and the dominant human sequence type in New Zealand, ST474, was found almost exclusively in isolates from 1 poultry supplier [47, 48], indicating that poultry was a major contributor to human infection. A considerable reduction in human illness cases was observed following the introduction of performance targets based on enumerated levels of *Campylobacter* on poultry carcasses at the end of primary processing, and the imposition of escalating regulatory responses when targets were not met. Reduced contamination of broiler meat and the subsequent marked decline in human cases was attributed to a variety of interventions, including improvements in hygienic practices throughout production and processing [21]. The substantial decline in human cases in New Zealand resulted in considerable savings to the country's economy [49]. Although the reduction in human illness in New Zealand is impressive, and lessons can be learned from the development and application of science to inform policy, it is difficult to extrapolate this success to other parts of the world. Prior to 2007, New Zealand had an extremely high incidence and unique epidemiological patterns, and even after marked improvements, the incidence is still high compared to other parts of the world.

CONCLUSIONS AND FUTURE DIRECTIONS

It is very difficult to keep broiler flocks *Campylobacter* free till the slaughter age, and there are no effective and technically implementable tools to reduce the colonization levels under field conditions. Generic interventions in the slaughterhouse are not yet available, and site-specific improvement of slaughter hygiene is a high priority. Risk assessment studies were the basis of a paradigm shift in the last decade. Where the aim in the past was to produce *Campylobacter*-free products, efforts in the future will aim for low levels of contamination—and this will require consumers to accept some level of risk and to take appropriate precautions. Elimination of highly contaminated products could have a considerable impact on the disease burden of *Campylobacter*. Improved slaughter hygiene in combination with treatment (eg, cooking) of highly contaminated

products should be part of a multilevel approach that should ultimately also include on-farm interventions.

Notes

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