Canine infectious diarrhoea: *Campylobacter,* a conundrum in dogs

K Bojanić[1], A Midwinter[1], P Biggs[1], E Acke[2]
[1] Infectious Disease Research Centre (IDReC)
[2] Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North

Introduction

Campylobacter-associated enteritis in dogs is, as in humans, an intestinal infection transmitted through faeco-oral routes by direct contact or through contaminated food, water or fomites. The disease is predominantly sporadic and most commonly presents as a self-limiting enteritis not requiring antimicrobial treatment (Fox 2006). The *Campylobacter* genus is relatively diverse but the enteric disease in dogs and humans has mostly been attributed to *C. jejuni*. Other species have also been implicated as potential pathogens and recent evidence suggests these may be underrepresented, mostly because of limitations of the currently applied methods in routine diagnosis of human campylobacteriosis (Moore *et al.* 2005).

In contrast to humans, dogs seem to have a less severe form of the disease but the clinical importance of *C. jejuni* and other 'emerging' *Campylobacter* spp. in dogs remains unclear. The questioning of their pathogenic role in infectious diarrhoea stems from discordant and equivocal findings of the few published experimental challenge experiments, and a number of clinical and epidemiological studies. However, the importance of *Campylobacter* spp. in dogs is not limited to their pathogenic potential to canines; public health aspects are also relevant. Contact with dogs or dog ownership has been repeatedly identified as a risk factor for people to become infected with *Campylobacter* spp. (Domingues *et al.* 2012), the most common cause of bacterial gastroenteritis in humans in the developed world. Research also shows that dogs may be important in the population biology of certain *Campylobacter* spp. The aim of this lecture is to provide a review of *Campylobacter* spp. in dogs, the importance in dogs from a public health perspective and to present new data on *Campylobacter* spp. in New Zealand pets.

The *Campylobacter* genus

Campylobacter species are non-spore forming, Gram-negative, small bacteria appearing as spiral or curved rods. Most of the species possess bi-polar flagellae that are responsible for a characteristic darting motility though some species are not motile (e.g. *C. gracilis*). The *Campylobacter* genus is part of the *Campylobacteraceae* family within the Epsilon class of the Proteobacteria phylum. There are over 30 species within the *Campylobacter* genus but the species of most importance to veterinary and human medicine are *C. jejuni*, the most frequent cause of bacterial gastroenteritis in people; and *C. fetus*, the causative agent of abortion in cattle and sheep. While some *Campylobacter* species are primary pathogens for certain host species, overall they are commonly present in the intestinal tract, oral cavity and reproductive organs of people and animals.

Campylobacter spp. have a limited metabolic capacity and require specific culture conditions which are associated with their fastidious and slow growth. The particular environmental conditions required for (presumably optimal) growth include microaerobic atmosphere (reduced oxygen, usually to 5%, higher CO_2, usually 10-15% and for some species addition of H_2), and an incubating temperature between 35-42°C (Nachamkin *et al.* 2000). Bacterial culture is considered a gold standard for the detection of *Campylobacter* spp. but even within the *Campylobacter*

genus there is a vast diversity in growth requirements between species. Consequently, numerous different culture methods have been developed and improved culture methods are still an active area of research. For instance, in order to facilitate isolation of *Campylobacter* spp. or to supress growth of background microflora, enrichment steps, media that contain antimicrobials and filtering techniques have been developed. Currently, the most commonly employed culture methods in diagnostic laboratories use media containing antimicrobial agents.

To date, the culture methods most commonly used in human diagnosis are directed at and/or optimised for the isolation of *C. jejuni* and *C. coli,* which are considered the most important pathogenic species in people and dogs. On the other hand, non-*jejuni/coli Campylobacter* spp., such as *C. upsaliensis*, have also been implicated as potential pathogens in people but not in dogs. These 'emerging' *Campylobacter* pathogens are usually susceptible to the antimicrobial agents commonly used in selective media or require some adaptation of standard culture protocols (Lastovica 2006). As these modifications are not necessary for the isolation of *C. jejuni/coli*, are cumbersome and increase costs and time-to-results, they are not commonly employed. This causes a certain degree of diagnostic bias and is generally accepted to be responsible for an underestimation of clinical significance and importance of non-*jejuni/coli Campylobacter* species in people. Likewise, investigations of animals and the environment are subjected to the isolation bias of culture methods and may skew the diversity of *Campylobacter* species observed.

The importance of *Campylobacter* spp. to dogs

Campylobacter jejuni was first isolated from dogs in 1977 in the UK (Skirrow 1977). Since then many other *Campylobacter* spp. have been detected in canine faeces but the most common species have been *C. jejuni, C. coli* and *C. upsaliensis* (Marks *et al.* 2011); the latter being the most frequent in reports where speciation was performed on a molecular basis. All of the species that have been detected in dogs have been observed in dogs with and without diarrhoea and factors that lead to development of clinical signs have not been elucidated.

Epidemiological studies

Most of the epidemiological studies investigating *Campylobacter* spp. in dogs have had a cross-sectional design. These studies have shown the prevalence rates of *Campylobacter* spp. in dogs to range from 0 to 78%. With such variability observed it is important to note that many of the published studies are not directly comparable and there are a number of reasons that could explain this wide variability. Apart from the dog's health status (presence of clinical signs), the differences could also be explained by the different populations sampled with regard to the age of animals, source of animals or their environment (e.g. household pets, stray, kennelled, clinical cases etc.), geographic location or season of the year. Likewise, the studies have varied in the design and methods, with different type of sample or its' transport (swabs, whole faeces, refrigeration etc.), diagnostic test (various culture methods, nucleic-acid based tests etc.), sample size etc. The prevalence range could also be related to different degrees of exposure and the susceptibilities to infection/colonization of the individual animals under test. These differences can significantly limit generalisation of the results and make comparisons between the studies extremely difficult but despite this there are certain associations identified in a number of them.

The possible association of *Campylobacter* spp. with clinical signs in dogs is the most important question from a canine health perspective. Several studies have reported a positive association of faecal carriage of *Campylobacter* spp. and presence of clinical signs (Ferreira *et al.* 1979, Blaser *et al.* 1980, Fleming 1983, Fox *et al.* 1983, Nair *et al.* 1985, Burnens *et al.* 1992, Torre and Tello 1993, Sokolow *et al.* 2005, Carbonero *et al.* 2012) but the majority of studies have not (Rossi *et al.* 2007, Hosie *et al.* 1979, Bruce and Ferguson 1980, Bruce *et al.* 1980, Prescott and Bruin-Mosch 1981, Simpson *et al.* 1981, Bruse and Fleming 1983, Gondrosen *et al.* 1985, Adesiyun *et al.* 1997, Baker *et al.* 1999, Lopez *et al.* 2002, Hackett and Lappin 2003, Modolo and Giuffrida 2004, Workman et al 2005, Tsai *et al.* 2007, McKenzie *et al.* 2010, Parsons *et al.* 2010, Leonard *et al.* 2011, Kumar *et al.* 2012), or instead they have reported an inverse association with the isolation rate being higher in healthy rather than from dogs with diarrhea (Cave *et al.* 2002). These findings are in contrast to experimental challenge studies and clinical case reports and raise the question of the significance of the pathogenic potential of *Campylobacter* spp. in pets. Other factors may be needed for clinical signs to develop and in this regard *Campylobacter* spp. could be secondary, opportunistic pathogens in dogs. Proposed factors that would predispose dogs to develop clinical signs could include co-infections with other bacterial, viral or parasitic agents (Holt 1980, Sandstedt and Wierup 1980, Jorgensen 1981, Prescott and Bruin-Mosch 1981, Fleming 1983, Fox *et al.* 1983, Olson and Sandstedt 1987, Misawa *et al.* 2002, Workman *et al.* 2005, Guest *et al.* 2007). Investigations into non-infectious factors have been

mostly centred on possible stress or the animal's health status affected by their environment (e.g. shelters and kennels), pregnancy, concurrent non-infectious diseases and immunosuppression. In anecdotal reports and case series in dogs, more severe illness has been observed and chronic cases of diarrhoea have also been attributed to *Campylobacter* spp. The evidence for pathogenic potential in clinical cases is mostly supported by the lack of other identified causes of diarrhoea and the resolution of clinical signs and faecal shedding following antimicrobial treatment (Hosie *et al.* 1979, Fleming 1983, Fox *et al.* 1983, Boscato and Crotti 1985, Fox *et al.* 1985, Olson and Sandstredt 1987, Brown *et al.* 1999). It is important to note that the cause of disease is presumed, not proven, as antimicrobial therapy, no matter how narrow-spectrum, is still non-selective and successful therapy may be due to elimination of unidentified agents that have coexisted with the *Campylobacter* organisms that were the only one detected.

The majority of epidemiological studies have shown an increased prevalence of *Campylobacter* spp. in younger dog groups

(Acke *et al.* 2009, Blaser *et al.* 1980, Fleming 1983, Nair *et al.* 1985, Burnens *et al.* 1992, Torre and Tello 1993, Hald and Madsen 1997, Workman *et al.* 2005, Guest *et al.* 2007) but an increase in prevalence rate as the dogs mature has also been reported (Hald *et al.* 2004). The decrease in prevalence as the dogs mature has been proposed to be due to frequent (re)exposure and the development of acquired immunity while being protected by maternally derived antibodies (Fox 2006). Increased incidence and evidence of seroconversion as animals mature has been documented in puppies and this finding has positively correlated with an increased incidence of *Campylobacter* spp. being shed in their faeces (Newton *et al.* 1988). This study was conducted in a closed dog breeding facility where campylobacteriosis was endemic and no external dog had been introduced to the facility for 9 years. The dam was presumed to be a source of exposure for the pups as it was observed that the dam had negative cultures during early pregnancy but was positive at the time of birth of her pups and during lactation. Other dogs as a source of exposure for young dogs have been supported by a longitudinal study in a shelter environment. It was reported the puppies reared with adult dogs have an increased incidence of faecal carriage of *Campylobacter* spp. but remained negative if contact with adults was not allowed (Buogo *et al.* 1995). However, that study also reported newly acquired colonization of pups has never been associated with the development of clinical signs.

Most of the studies were in agreement that the prevalence of *Campylobacter* spp. was higher in stray or sheltered/kennelled animals when compared to the prevalence in household pets (Bruce *et al.* 1980, Bruce and Fleming 1983, Torre and Tello 1993), but strong disagreement in this association has been also observed (Ojo 1994). It has been argued that dietary factors, stress associated with shelters/kennels and increased close contact and exposure are responsible for differences between shelter/kennelled and household dogs (Acke *et al.* 2006). In stray dogs, a longitudinal study undertaken upon initial impoundment showed a significant increase in the isolation rate of *C. jejuni* at days 5-7 compared to admission at day 1 which could be related to all of the above factors (Burnie *et al.* 1983). In the household dog population, some studies have shown there is an increased risk of dogs shedding *Campylobacter* spp. when more dogs are present in a household, whereas other studies have not confirmed this. These latter studies, and the above studies in pups, imply that direct/close contact between animals may be an important transmission pathway of *Campylobacter* spp. for dogs, whereas for people, person-to-person contact is considered a rare source of infection (Moore *et al.* 2005).

Only few longitudinal studies have been performed in dogs. All studies were in agreement that the majority of dogs have been observed to shed *Campylobacter* spp. with no association with diarrhea (Newton *et al.* 1988, Hald *et al.* 2004, Parsons *et al.* 2011). The observed pattern of excretion is mostly intermittent although persistent long-term excretion may occur. No association of any *Campylobacter* spp. with diarrhoea was observed and it is possible that a carrier state exists or that *Campylobacter* spp. are part of the normal intestinal flora in dogs. However, two studies showed there is a different pattern between faecal carriage of *C. jejuni* and that of *C. upsaliensis* in dogs (Hald *et al.* 2004, Parsons *et al.* 2011). *C. jejuni* was more commonly isolated on single occasions whereas *C. upsaliensis* was frequently isolated in successive samples during the two year follow-up period though diarrhoea was not associated with either species (Hald *et al.* 2004). The pulse-field gel-electrophoresis genotype profiles showed that different *C. jejuni* genotypes were recovered from different dogs but within the individual dog *C. jejuni* was isolated in vast majority on single occasions. Conversely, the same or closely related *C. upsaliensis* genotypes were present in several dogs and within the individual dog, the same or closely related genotypes were recovered for long periods. The significance of this finding is uncertain but it could imply dogs act as a reservoir of *C. upsaliensis*. In support of this view, *C. upsaliensis* has, apart from sick humans, almost exclusively been

isolated from dogs (and to a lesser extent cats) but this association should not be taken as an evidence of proof. Lastly, longitudinal studies have shown that the collection of multiple samples from an animal may aid in the successful isolation of *Campylobacter* spp. from faeces.

Experimental challenge studies

Few experimental infection studies have been performed in dogs and those were conducted in the late 70's and early 80's; results confirmed the pathogenic potential of *C. jejuni*. Various age groups of dogs were infected: conventionally reared puppies (Prescott and Karmali 1978), gnotobiotic puppies (Prescott *et al.* 1981), juvenile dogs (Olson and Sanstedt 1987), adult dogs (Macartney *et al.* 1988), multiple age groups, or age not reported (Kang 1985, Diker and Unsuren 1990, Boosinger and Dillon 1992). The *Campylobacter* spp. isolates used for the challenges in these studies were isolated from human cases, canine "cases" or healthy pigs. The pathogenic potential was supported by the clinical and histopathological changes observed. Histopathological changes usually affected the entire intestine and included loss of goblet cells, stunting of the villi, attenuation and erosions of the epithelia with hypertrophy of the glandular mucosa, hyperplasia of the lymphoid tissue in the mucosa and haemorrhagic and neutrophil infiltration of the lamina propria (Prescott *et al.* 1981, Macartney *et al.* 1988). Some studies assessed haematological and biochemical profiles in infected dogs but no changes were observed in one study (Olson and Sandstedt 1987) while in another study affected puppies had increases in leukocyte and erythrocyte counts and serum concentrations of urea which was presumed to be due to systemic inflammatory response and/or dehydration (Diker and Unsuren 1990). Clinical changes were generally mild to moderate (Prescott *et al.* 1981, Olson and Sandstedt 1987, Macartney *et al.* 1988) and rarely severe (Kang 1985, Diker and Unsuren 1990, Boosinger and Dillon 1992). Duration of clinical signs was usually short and *Campylobacter* bacteria were recovered from the faeces of challenged dogs for several days to weeks, depending on duration of follow-up.

Two studies evaluated the effects of antimicrobial therapy on faecal shedding of *C. jejuni*. One study evaluated antimicrobial treatment in orally challenged adult dogs (Boosinger and Dillon 1992). In this study 6 out of 19 adult dogs did not shed *C. jejuni* in their stools during a 28 day follow-up period and 12 dogs that had positive faecal cultures had slightly softer stools for two to three days but otherwise appeared normal. The twelve adult dogs that shed *C. jejuni* for at least eight days were given erythromycin (10mg/kg) or tetracycline (20mg/kg) three times a day for seven days. Faecal cultures were negative for *C. jejuni* in all 12 treated dogs by post-treatment Day 2, and weekly faecal specimens remained culture negative for four weeks in all dogs. Another study compared the efficacy of a 12-day long oral erythromycin and chloramphenicol treatment on faecal shedding of *C. jejuni* in a naturally infected laboratory colony of English Foxhounds (Montfort *et al.* 1990). Treatment with erythromycin prevented shedding of *C. jejuni* by the fourth day of treatment in all nine dogs whereas chloramphenicol was associated with a reduction in shedding from 100% to 57% by the ninth day of treatment. However, within nine days of the discontinuation of antimicrobial treatment, *C jejuni* was isolated from all chloramphenicol- and 89% erythromycin-treated dogs but it remains unexplained as to whether this was a new infection or a relapse of the previous one.

Almost all of the above experimental studies have been undertaken with a small number of animals (3-6 per test run) which limits the significance of the results. However, the most common findings in all studies are: (i) clinical signs can be induced by *C. jejuni* (ii) not all dogs develop clinical signs (iii) clinical signs are usually of short duration (1-3 days) and mild to moderate (iv) infection challenge results in faecal carriage of bacteria which can last, albeit intermittently, for several days to weeks (v) pathological findings do not necessarily correlate with presence of clinical signs and (vi) intestinal invasion does not seem to be a feature of the pathogenesis. *C. coli* was evaluated by only one study and the pathogenic potential was documented in dogs (Diker and Unsuren 1990). Also, only one study evaluated *C. upsaliensis* in dogs but reported virtually no evidence of pathogenicity (Olson and Sandstedt 1987).

The experimental studies also suggest there are probably significant differences in the pathogenicity of *C. jejuni* strains as well as variable susceptibility of the hosts. The host susceptibility could be related to age as, although all age groups could be affected there appears to be an increased susceptibility in young animals. In addition, the health status, exposure history, maternally acquired immunity and intestinal flora (gut microbiome) may also influence the host's predisposition to the disease. With regard to the varying pathogenicity of strains there is only one study that reported an association between particular *C. jejuni* genotypes and clinical signs in dogs (Amar *et al.* 2014). In that study, multi-locus sequence typing (MLST), a widely used genotyping method was used to

characterise *C. jejuni* isolates. It was observed that ST-45 was significantly more prevalent in diarrhoeic than non-diarrhoeic Swiss dogs. This finding is possibly spurious due to the small sample size and zero occurrence of ST-45 in non-diarrhoeic dogs in that study as ST-45 has been frequently detected in non-diarrhoeic dogs in UK (Parsons *et al.* 2009), Netherlands (Mughini Gras *et al.* 2013) and in New Zealand (Bojanic *et al.* 2013).

The importance of dogs to *Campylobacter* spp.

Campylobacter infection is zoonotic but can be acquired from many sources and through various transmission routes. Dogs are a common companion animal around the world and in New Zealand the dog ownership rate is among the highest in the developed world (Mackay 2011). This could imply that dogs may be important to the epidemiology of campylobacteriosis in people. Indeed, contact with dogs (or ownership) has been repeatedly shown by classical epidemiological studies as a risk factor for the disease in people. In a case-control study performed in New Zealand (Eberhart-Phillips *et al.* 1997) the odds for having campylobacteriosis (adjusted for sex, age and telephone prefix) were calculated to be 2.67 higher for people owning a puppy than for those not owning a puppy. In addition, a recent meta-analysis of case-control studies of sporadic campylobacteriosis in people has estimated contact with pets to confer 1.96 higher odds for acquiring the disease than having no such contact and no significant publication bias was observed for this risk factor (Domingues *et al.* 2012).

There have been several studies using molecular epidemiological approaches that investigated dogs as sources of infection or risk factors for contracting the disease. In New Zealand, the 'Manawatu *Campylobacter* sentinel surveillance study' has been conducted for the purposes of source attribution modelling of human campylobacteriosis cases. The study identified that between 0.6 and 6.3% (depending on the models used) of human cases could be attributed to dogs and cats as a source of infection (French *et al.* 2011). In that study MLST was also performed for the purposes of genotyping *C. jejuni* isolates. Other researchers using MLST have also observed associations of *C. jejuni* isolates from dogs with isolates from human *Campylobacter* cases. Studies in the UK (Parsons *et al.* 2009) and Switzerland (Amar *et al.* 2014) reported that the majority of MLST genotypes detected in dogs were also detected in human patients. In another Swiss study, source attribution modelling was conducted and similarly to New Zealand, 8.6% of human cases were attributed to dogs as a source of infection (Kittl *et al.* 2013). A recent Dutch study identified that dog and particularly puppy owners were at increased risk of infection with pet-associated *C. jejuni* genotypes (MLST). In that study sampling of dogs from households where a person was ill with campylobacteriosis was performed. In 2 out of 68 cases a pet and its owner were infected with an identical genotype which was a significantly higher rate from the estimates of occurrence by chance; 0.134 out of 68 cases (Mughini Gras *et al.* 2013). However, sampling of dogs was performed after people developed clinical signs thus, sources of infection may have been common for people and dogs and transmission between them (dog to person or person to dog) could not be established.

With regard to transmission between dogs and people it is important to note that contact with dogs (or ownership) is a broad epidemiological variable and does not necessarily imply that infection has been acquired directly from the dog. Many dog-related activities or associated practices may lead to potential exposure of dog-owners placing them at increased risk for disease. For instance, these could be related to food which is a common vehicle for *Campylobacter* infection; type of dogs diet (e.g. raw meat based diets or treats), location where dogs are fed or where dog food is prepared or stored that could potentially enable cross-contamination of surfaces etc. Exposures related to potential direct transmission from dogs to people may be dependent on the degree of close contact between dogs and people such as allowing licking of hands and/or face, sleeping on the bed etc. On the other hand, higher risks could be related to different practices, activities and behavioural traits that are not directly dog-related but that dog-owners more frequently than non-owners engage in (inside and outside of their households) and thus, put them at a higher risk for disease. A recent study of characteristics of dog owners in New Zealand identified that out of 727 respondents (42% response) just under a third reported to currently own dogs, a third never owned dogs while over a third had some history of dog ownership (Flint *et al.* 2010). The study reported dog owners are likely to be aged between 18 and 55 years, educated to secondary school level or above, live in a rural or suburban area, be married or in a de-facto relationship with children over the age of one year, and consider themselves to be of positive character. Clearly, all of these variables could be important in epidemiology of any infectious diseases, including campylobacteriosis.

From the above considerations with regard to epidemiology of disease it is obvious that there are many difficulties in explaining how exactly contact with or owning a dog places us at increased risk for developing campylobacteriosis.

There are many potential pathways which most likely have varying degrees of risk associated with them and our current understanding of these processes is limited. The research shows there is a need to increase awareness of public health risks associated with pets. A recent study reported that only 40% (102/255) of dog-owners recalled ever receiving information on pet-associated zoonotic diseases or precautions to reduce the risk of disease (Stull *et al.* 2013). In most of the dog-owning households many high risk practices were frequently noted such as feeding dogs in the kitchen, feeding dogs high risk food items or close contact such as sleeping in a child's bed or licking their face and over half of dog-owning households had one or more potentially higher risk individuals (<5 or >65 years of age or immunocompromised). Another important finding is that for households with higher risk individuals or those that recalled receipt of information on zoonotic diseases, no associations with the use of different or additional husbandry or infection control practices were observed compared to other households. In another study 70% of pet owners reported they were comfortable with their current understanding of zoonotic diseases acquired through contact with pets and 65% were comfortable with their understanding of ways to prevent disease (Stull *et al.* 2012). Public health is a multidisciplinary area and educational efforts to increase awareness of health risks and the means of controlling or reducing these risks are to be shared by human, veterinary and public health professionals. Lastly, raising general awareness and improving knowledge of practices relating to public health associated with pets has far greater benefits since more than 70 pathogens of companion animals are known to be transmissible to people.

Summary of key points

Several decades of *Campylobacter* research in dogs has given us more understanding of the epidemiology and potential for disease and while further investigations are needed to elucidate exact mechanisms of development of disease, the key features can be summarised as follows:

- dogs are frequently exposed to many *Campylobacter* spp. which may be detected in healthy and dogs with diarrhoea.
- *C. upsaliensis* and *C. jejuni* have been the most commonly isolated species.
- pathogenic potential has been documented to date only for *C. jejuni* and to lesser extent *C. coli* but further studies are required and a mere isolation/detection should not be taken as the cause of clinical signs.
- clinical signs are mostly mild to moderate, of short duration and do not require antimicrobial treatment unless there is evidence of systemic involvement with more severe clinical signs or the signs are chronic or prolonged.
- shedding of *C. jejuni* is of relatively short duration (few days to few weeks) whereas *C. upsaliensis* can be shed for long periods (more than a year).
- previous *Campylobacter* infections or antimicrobial treatments do not prevent future recurrences.
- contact with and/or owning a dog is a proven risk for contracting disease in people but dogs are less important sources of infection compared to food- and water-borne sources.
- there is a need to raise awareness of and in providing a means of reducing the public health risks associated with pets for pet owners and the general public especially people at higher risk of developing disease.

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