Pathogen Survival Trajectories: An Eco-Environmental Approach to the Modeling of Human Campylobacteriosis Ecology

Chris Skelly[1] and Phil Weinstein[2]

[1]Public Health Intelligence, Public Health Directorate, Ministry of Health, Wellington, New Zealand; [2]Department of Public Health, Wellington School of Medicine, The University of Otago, Wellington, New Zealand

Campylobacteriosis, like many human diseases, has its own ecology in which the propagation of human infection and disease depends on pathogen survival and finding new hosts in order to replicate and sustain the pathogen population. The complexity of this process, a process common to other enteric pathogens, has hampered control efforts. Many unknowns remain, resulting in a poorly understood disease ecology. To provide structure to these unknowns and help direct further research and intervention, we propose an eco-environmental modeling approach for campylobacteriosis. This modeling approach follows the pathogen population as it moves through the environments that define the physical structure of its ecology. In this paper, we term the ecologic processes and environments through which these populations move "pathogen survival trajectories." Although such a modeling approach could have veterinary applications, our emphasis is on human campylobacteriosis and focuses on human exposures to *Campylobacter* through feces, food, and aquatic environments. The pathogen survival trajectories that lead to human exposure include ecologic filters that limit population size, e.g., cooking food to kill *Campylobacter*. Environmental factors that influence the size of the pathogen reservoirs include temperature, nutrient availability, and moisture availability during the period of time the pathogen population is moving through the environment between infected and susceptible hosts. We anticipate that the modeling approach proposed here will work symbiotically with traditional epidemiologic and microbiologic research to help guide and evaluate the acquisition of new knowledge about the ecology, eventual intervention, and control of campylobacteriosis. *Key words:* aquatic environments, *Campylobacter*, campylobacteriosis, disease ecology, eco-environmental modeling, ecologic filters, feces, pathogen survival. *Environ Health Perspect* 111:19–28 (2003). [Online 7 November 2002] doi:10.1289/ehp.5312 available via *http://dx.doi.org/*

Campylobacteriosis has been the most common enteric disease in New Zealand since at least the early 1990s (*1*), with national notification rates currently exceeding 230 cases per 100,000 persons and regional notification rates exceeding 300 per 100,000 (*2*). In the United States, the *Campylobacter* spp. pathogens are responsible for the highest incidence of disease of any of the enteric pathogens under surveillance, with between 17 and 25 cases per 100,000 persons across FoodNet sentinel sites from 1996 to 2000 (*3*). California is the FoodNet site with the highest incidence of campylobacteriosis, with between 30 and 60 cases per 100,000 persons over the same period (*3*). However, these are probably conservative estimates of disease incidence, as enteric disease surveillance is known to underestimate incidence considerably (*4*). Despite its widespread incidence, the ecology of campylobacteriosis remains elusive, and suitable ecologic or environmental transport models have yet to be developed. In this review we attempt to lay a foundation for the eco-environmental modeling of human campylobacteriosis.

An eco-environmental model of human disease is an attempt to describe both the ecology (dynamics of the disease, including pathogen filters) and environments (including structure and vectors) through which pathogens must traverse to obtain new hosts. A system, as in the usage "ecosystem" has been defined in the biologic and climatologic literatures as interlinked flows of energy, momentum, and matter (*5,6*). However, within the public health literature, the term "ecology" is used in different ways, most notably in the context of ecologic analysis, which describes an aggregated scale of analysis, usually in terms of geographically defined human populations (*7,8*). Other researchers apply the terms "ecology" and "ecosystem" to the construction of conceptual models of the interdependency between human disease and the natural environment (*9,10*). The linkage between human society and natural ecosystem health is used as a means to broaden the scope of policy development with respect to assessing public health risk, e.g., cutting down trees in a water catchment will decrease water quality and worsen enteric disease outcomes (*11,12*). However, these models are devised entirely for the purpose of conveying linkage concepts and not of simulating possible outcomes or the mechanisms of exposure that these linkages might entail.

Modeling must eventually move beyond conceptualization to support quantitative assessment of environmental linkages. Eco-environmental disease modeling is the quantitative approach proposed here to assist in the development of understanding with regard to the interdependencies between human health and natural systems. Of the few researchers who have begun to move in this direction, most have been associated with disease vector modeling, the impacts of climate change, or a combination of these two modeling efforts (*13–16*). Although the desirability of incorporating natural ecosystems into the study of human disease ecology has been identified (*17,18*), little progress appears to have been made with regard to model development. An eco-environmental model of campylobacteriosis needs, at a minimum, to capture *a*) the ecologic dynamics that act to filter *Campylobacter* pathogens from the environment, *b*) the temporal movement of pathogens through various environments, and *c*) environmental temperature that influences pathogen survival time.

The predominant focus of disease modeling of the past has been centered on the concepts of host population dynamics and the mechanisms of person-to-person spread (*19*). This is discussed further in the next section. However, in this paper we propose that an alternative modeling approach focusing on eco-environmental processes is required if we are to apply computer-modeling techniques to the understanding of enteric pathogens such as *Campylobacter*. This approach attempts to pull together the epidemiologic and microbiologic literature to provide insight into the ecology of campylobacteriosis. After a brief review of the major ecologic dynamics and environmental vectors of this disease, we propose

the structure of an eco-environmental model for campylobacteriosis. In this paper, we plan to lay the necessary groundwork for the future development of quantitative eco-environmental models for campylobacteriosis and other enteric diseases.

Approaches to Modeling Human Disease Ecologies

Models are human constructs that are superimposed upon real-world complexity. Therefore, a model can be described as a device used to simplify an object of study. Models come in all shapes and sizes and are used for many purposes. However, researchers have become used to the idea of using quantitative computer-based simulation models, particularly stochastic models used to describe relationships, e.g., regression models. Another type of model that may be less familiar to epidemiologists and public health professionals is the dynamic or process model.

Dynamic modeling underlies the proposed eco-environmental approach to campylobacteriosis. This type of modeling focuses on the components of the system, which drive important ecosystem dynamics. For example, changes in environmental temperature appear to play an important role in the survival of *Campylobacter* outside the animal host. Consequently, temperature is a variable important to the process of pathogen survival (*20,21*). This dynamic modeling approach is well entrenched in the earth sciences (*6*) and disease vector modeling (*13*). Within the practice of dynamic modeling, a number of tools have been used, including deterministic modeling, stochastic modeling, and more recently, fuzzy logic, neural networks, genetic algorithms (*22*), implementation of Markov Chain Monte Carlo in application of Bayesian methods (*23*), and quantitative risk assessment methodologies (*24*). Regardless of the tools used, the focus should be on those components known to contribute to the dynamics of the system being modeled. Ultimately, modeling should lead to the development of a better understanding of those dynamics and refocus attention on areas where knowledge is lacking. The use of dynamic modeling in the study of human disease ecology has led to significant gains in knowledge that can be used to tackle new problems such as understanding potential impacts from climatic change (*25*). However, the modeling of disease ecology has yet to be applied to campylobacteriosis or other enteric diseases.

Anderson and May (*19*) have written what is arguably the single most important text on the modeling of human disease dynamics. Yet, enteric diseases such as campylobacteriosis are not covered in this important work. The reason for this omission can be surmised from their recollection that

Our interest in the work described in this book originally grew out of our attempts to understand the extent to which parasites–broadly defined to include viral, bacterial, protozoan, and fungal pathogens along with the more conventionally defined helminth parasites–regulate the numerical abundance or geographical distribution of non-human animal populations (*19*).

Although without doubt their contributions are now focused on animals of the two-legged variety, enteric diseases have not in general "regulated the abundance or geographical distribution" of animals, particularly humans, at least in the developed world. Even in developing countries where mortality from enteric disease is high compared with other health issues, the availability of enteric disease interventions such as oral rehydration therapy (*26*) and engineering solutions that provide clean water have perhaps reduced interest in developing models to improve knowledge. There might be a greater sense of urgency in understanding the campylobacteriosis disease ecology if relatively simple interventions were known to be available and morbidity and mortality more severe. The modeling of human disease ecology has instead focused on the person-to-person spread of diseases between susceptible and infective hosts using mathematical devices such as the basic reproductive rate, R_0, for diseases with more dire outcomes (*19*).

R_0 is the principal mechanism used to model the number of secondary host infections that are produced from one primary infection. This is a particularly useful approach to take when the mechanism(s) of spread and environmental pathways of the pathogen are well understood, as is the case in person-to-person spread and some vector-borne diseases. However, it poses a problem when the environmental pathways of the pathogen are only partially understood, as is the case with most enteric disease (*27*). Modeling of enteric disease has consequently been limited to those enteropathogens whose primary mechanism of spread is person to person rather than those where animal reservoirs are the primary source of pathogens (*26–29*). Indeed, we have been unable to find any evidence of an attempt to model campylobacteriosis or similar enteropathogen zoonoses.

The way forward may be to construct a model disease ecology from the perspective of pathogens trying to survive until they find their next host, rather than the more traditional host-centric models typified in population dynamics-based modeling. Modeling pathogen survival as pathogen survival trajectories with various ecologic filtering processes (e.g., cooking food), intermediate environmental vectors (e.g., flies or food preparation surfaces), and associated constraints to survival (e.g., environmental temperature) constitutes

an eco-environmental approach. This might also be termed a "Lagrangian" model that follows the flow of a particular group of pathogens through the environment, whereas traditional models calculate fluxes at fixed points within the model (e.g., time or space). The advantage of this Lagrangian approach is that it directly focuses on the unknowns of greatest interest (i.e., the survivability of pathogens as they move through the environment to their next host).

The Ecology of Campylobacteriosis

Although campylobacteriosis is the most common known cause of gastrointestinal illness, our understanding of its ecology is incomplete. Overall, what we do know is that the *Campylobacter* spp. pathogens replicate almost exclusively within the intestinal tract of warm-blooded animal hosts (*20*), within a narrow temperature range of approximately 32–45°C (*21*). Pathogen dispersal from its animal host is through the excretion of feces or the contamination of an animal's carcass by the intestinal contents during slaughter. It is this contamination of meat products that is believed to be the major source of campylobacteriosis in the human population (*30*). This belief is supported by case–control studies that have identified the consumption of untreated water, unpasteurized milk, and certain meats, often poultry, with the additional risk of campylobacteriosis (*31–35*).

Even if we accept that the major mechanism for the spread of campylobacteriosis is through food contamination, our understanding is incomplete. What is it about animal management practices and food processing systems that allow this pathogen to be so widely spread? Food preparation practices, which are the final safety check, do not appear to effectively remove *Campylobacter* pathogens. Why? The seasonal oscillation in human disease incidence is one of the most remarkable features of campylobacteriosis that we observe through human disease surveillance systems (Figure 1). This seasonal pattern of raised summer incidence appears in all countries where human campylobacteriosis is under surveillance (*36*).

There are at least two possible food-borne explanations for the observed seasonal oscillation in incidence. The first explanation is that during the warmer summer months, human exposure to the pathogens increases through outdoor grilling. It is thought that this might reduce the likelihood of thorough cooking and also increase the possibility of cross-contamination on relatively crowded barbecue grills (*35,37*). A second explanation is seasonality in the number of animals with campylobacteriosis, which in turn drives the seasonality of human disease incidence (*38*).

However, there is contradictory evidence indicating that in some animal industries, carcasses may be contaminated throughout the year (*38*). Additionally, the seasonal increase in human cases has been acknowledged to precede seasonal rises in animal infections in some instances (*38*).

Non–food-related explanations for the seasonality of campylobacteriosis include the survival and consequent prevalence of *Campylobacter* in environmental reservoirs (*39,40*) and the seasonal effectiveness of the human immune system response (*41*). For a pathogen that is so difficult to culture in a laboratory, *Campylobacter* have been shown to have a rather remarkable capacity for survival in aquatic environments (*42*). Indeed, it appears that greater numbers of pathogens are found in aquatic environments during winter and spring periods because of the relatively lower water temperatures in winter (*43*). A potential relationship can be hypothesized between the seasonal accumulation of pathogens in the environment and the eventual rise in human disease during the following summer season. However, this is speculative, as we know of no direct studies of this potential relationship, and there are additional confounders such as the potential for increased

human exposure through summer recreational contact with water.

The human immune system is another variable with a seasonal oscillation, and is impaired with greater exposure to ultraviolet (UV) radiation (*41*). This establishes another possible explanation that variation in immune response supports a component of the seasonality in human disease incidence, where the annual summer peak in notifications coincides with the population's greatest exposure to UV radiation. The potential credibility for this mechanism has been established through the study of the role of the immune system in responding to campylobacteriosis and other enteric pathogens in a group of captive primates (*41*).

The viable but nonculturable (VNC) form of the *Campylobacter* pathogen has presented a major hurdle in developing an understanding of the disease ecology by limiting our ability to detect, classify, and quantify the *Campylobacter* pathogens in the environment. The literature on this topic of microbiologic techniques development is vast, and it is not reviewed here. Nonetheless, models will need to capture or account for our lack of knowledge stemming in part from our inability to see *Campylobacter* in the environment.

The physiologic role of the VNC form of *Campylobacter* is not clear, but its ability to use this form to survive in cold water has been demonstrated (*44*). Furthermore, there is some evidence that after surviving for considerable periods of time in aquatic environments, the passage of VNC *Campylobacter* through an animal host will restore it to its culturable form (*45*).

The dose–response relationship may also be an important component of the disease ecology of campylobacteriosis and may differ for various types and strains of the *Campylobacter* pathogen (*46*). The dose–response relationship for the number of pathogens required to cause disease is less certain than that required to cause infection. In one study, the greatest dose studied (1×10^8 pathogens) produced no disease in five nonimmune human subjects (*46,47*). A beta-Poisson model of the challenge studies of Black et al. (*46*) has been used to define a dose–response relationship for humans (*48*) and to assess the risk of consuming mussels (*49*). Although only a few challenge studies of human campylobacteriosis have been conducted, these studies do provide a starting point from which to base a modeling approach.

Although it is thought that many or even most cases of campylobacteriosis arise through the consumption of contaminated food and water, it is less clear how the pathogens move through the environment. The majority of campylobacteriosis cases appear sporadically and not in outbreaks, but there is an acknowledged occurrence of common-source milk (*50,51*) and waterborne disease outbreaks (*52–54*), which does nothing to clarify the disease ecology. The one mechanism of spread that can be modeled using established techniques is person-to-person spread, but this mechanism has not been widely implicated in the literature (*55*). Despite the many studies already published, uncertainty dominates our understanding of the ecology of campylobacteriosis, and this justifies an evaluation of the potential for applying dynamic modeling.

Pathogen Survival Trajectories: An Eco-Environmental Modeling Approach

An eco-environmental model for campylobacteriosis must focus on the environmental transmission pathways of the *Campylobacter* pathogen (Figure 2). This approach describes the ecology of campylobacteriosis from the perspective of a pathogen's survival as it moves through the environment—a survival trajectory. We use the pathogen's survival in the environment as the mechanism to quantify human exposure. Our lack of knowledge about pathogen survival hinders our ability to understand the ecologic dynamics and potential public health intervention points.
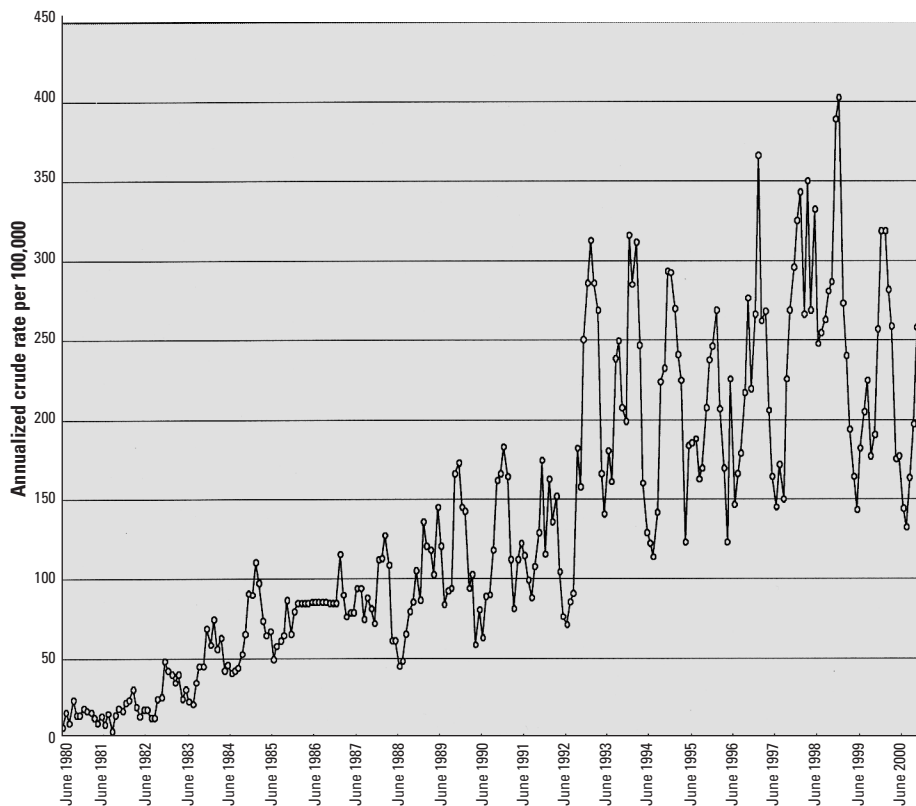

Figure 1. Seasonal pattern of campylobacteriosis in New Zealand. Aside from the steady rise in incidence, summer–winter seasonality dominates the temporal picture of campylobacteriosis in New Zealand, even from the period shortly after notifications were first recorded in 1980. Note that monthly data from 1986 were not archived [data from the Department of Heath (Wellington, New Zealand) records for before 1993 and from the New Zealand disease notification system (EpiSurv) for 1993 and later].

The *Campylobacter* pathogens replicate primarily within the intestinal tract of warm-blooded animals. Therefore, it is the postexcretion of pathogens that defines the ecology of campylobacteriosis, and all survival trajectories begin with pathogens being dispersed from animals through feces (Figure 2). Feces then serve as the primary environmental dispersal mechanism (Figure 2), including animals slaughtered for food processing, where the carcass is often contaminated by their *Campylobacter*-laden intestines. Secondary mechanisms of dispersion may occur, and all successful survival trajectories end with the new exposures (Figure 2).

There are three general nonoccupational pathogen survival trajectories: *a*) direct exposure to feces; *b*) exposure through food consumption, food processing, or food preparation activities; or *c*) exposure through aquatic environments (Table 1). These mechanisms, which all describe oral routes for pathogen exposure, have associated ecologic filters that provide natural public health intervention points. In turn, the pathogen burden with which each of these filters must cope depends upon environmental factors that control the size of the pathogen load that arrives at a filter point (e.g., rainfall, stocking density, speed and magnitude of runoff, proximity to water body). Grouping pathogen survival trajectories according to common environmental elements (Table 1) facilitates comparative ecologic risk assessments of pathogen survival and human exposure routes (Figure 2). It is worth noting that the above ordering of ecosystem components is in order of increasing risk, identified through case–control studies. It also appears, at least at face value, to be in increasing order of the complexity of the pathogen survival trajectory. In other words, what might appear to be the best survival prospect for *Campylobacter* pathogen, from epidemiologic studies, appears to be the least survivable. This is a consequence of the relatively greater number of ecologic filters a pathogen would need to traverse to find a new host and replenish its numbers.

From an ecologic perspective, direct exposure to feces or indirect exposure to feces through human-to-human contact or animal-to-human contact would appear to be the most likely survival trajectory (Figure 2). Feces, as the direct excretion of materials from the intestines of warm-blooded animals, must be the environments of greatest *Campylobacter* concentration outside their animal hosts. From feces through the exposure of the next animal host, *Campylobacter* numbers must decrease. Their survival depends only on reaching their next host before their number declines below what is required for an infective dose.

Feces of warm-blooded animals must therefore represent the environmental site of

greatest hazard. Animal hosts are many and varied, including birds and wild, domestic, and domesticated animals of all shapes and sizes as well as humans [Table 2 (*55–82*)].

There does not seem to be a shortage of *Campylobacter*-contaminated feces in the environment. From a modeling perspective, we might well consider the supply of pathogens
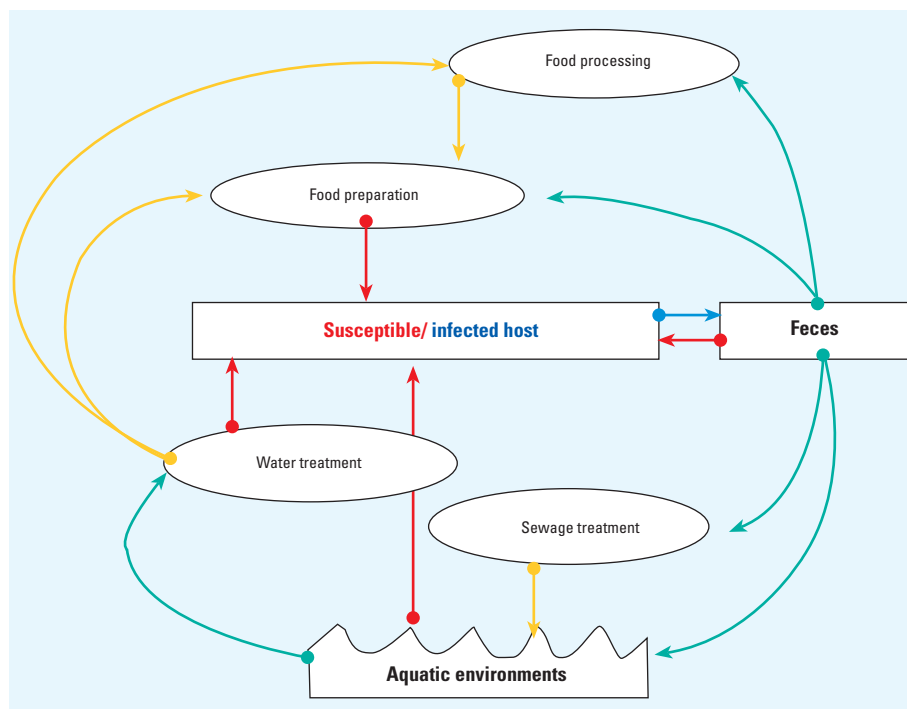

Figure 2. A generalized eco-environmental model of human campylobacteriosis, which is composed of four components: animal reservoirs/hosts, ecologic filters (ovals denoting processes), aquatic environments, and survival trajectories linking hosts, ecologic filters, and aquatic environments. Blue arrow, pathogens dispersed from animals through feces; green arrows, feces as the primary environmental dispersal mechanism; yellow arrows, secondary mechanisms of dispersion; red arrows, resulting new exposures.

Table 1. Components of the eco-environmental model required to explore the disease ecology of campylobacteriosis in humans exposed by means of the three general nonoccupational pathogen survival trajectories direct contact with feces, through food consumption and handling, and through the consumption of water and/or contact with aquatic environments.

Human exposures	Eco-environmental model variables	
	Ecologic filters	Intermediate environmental vectors
Direct exposure through feces	Personal hygiene	Survival in feces
Direct contact with human and/or animal feces		Survival on skin and hair surfaces
Person to person		
Animal to person		
Food		
Eating contaminated meat or cross-contaminated foods	Personal hygiene	Survival on human skin and hair surfaces
	Kitchen hygiene	
	Pathogen removal via effective storage and cooking processes	Survival on metallic, wood, and plastic surfaces
	Pathogen removal during meat processing	Survival on prepared food
	Infection control during animal rearing	
Aquatic environments	Safe recreational behaviors	Transport and deposition into aquatic environments
Untreated		Survival in aquatic environments
Swallowing contaminated water during recreation (unintentional) or drinking untreated water (intentional)	Reduction in non-point source pollution (domestic grazing management)	
	Sewage treatment	
Treated		
Drinking contaminated water through a community reticulation system	Water treatment	Survival in treated water environments

from feces to be infinite. Why is it, then, that epidemiologic studies and disease surveillance information do not suggest that either direct feces contact or indirect (human-to-human or animal-to-human) feces contact to be a major component of the disease ecology?

There may be at least two reasons why neither direct nor indirect contacts with feces are the major pathogen survival trajectories of *Campylobacter*. First, most human contact with animal feces is probably of an occupational nature in the agricultural and food

Table 2. Animal reservoirs of human *Campylobacter* pathogens from intestinal samples, fresh feces, or surfaces of freshly slaughtered carcasses.

Animal reservoirs	Proportion of animals infected	Pathogen load	Seasonality and other notable study features	References
Humans				
United Kingdom	Poultry workers: short-term (≤ 1 month) employees, one tested positive (*n* = 43); long-term employees, seven tested positive (*n* = 78)	—	Only one short-term worker had symptoms indicating longer-term immunity in workers	(56)
	Clearance from food handlers averaged 17–19 days			(55)
Chile	Children with diarrhea 16% (*n* = 190); healthy children 6% (*n* = 157)	—	Associated analysis of domestic pets: dogs 43% (*n* = 214); hens 67% (*n* = 150); ducks 73% (*n* = 100); pigeons 11% (*n* = 104)	(57)
Wild animals and domesticated pets				
United States	Thirteen orders of wild and domesticated birds 10% (*n* = 445)	—		(58)
	Young dogs with diarrhea infected with *C. jejuni*			(59,60)
Norway	Urban Oslo: crows 90% (*n* = 48); gulls 50% (*n* = 54); pigeons 4% (*n* = 71)	—	11 of 40 species tested positive for *C. fetus* spp. *jejuni*	(61)
	Nonurban coastal area: puffin 51% (*n* = 76); common tern 6% (*n* = 36); common gull 19% (*n* = 37); black-headed gull 13% (*n* = 53)			
	Migratory water fowl 35% (*n* = 445)	—	Another study found no evidence of *C. jejuni* in lakewater inhabited by over 600,000 water fowl	(62)
Japan	Crows 34% (*n* = 87); blue magpies 20% (*n* = 10); gray starlings 14% (*n* = 35); domestic pigeons 13% (*n* = 16); bulbuls 11% (*n* = 36); eastern turtledoves 2% (*n* = 62)	—	25% of gut contents of crows was human refuse	(63)
	Seashore crows (feces) 63% (*n* = 270); cemetery crows 46% (*n* = 230)		Considerable monthly variation in isolation rates was found	(64)
United States	Migratory birds: sandhill cranes 81% (*n* = 91); ducks 73% (*n* = 113); Canada geese 5% (*n* = 94)	—		(65)
Sweden	Migratory passerines 3% (*n* = 101)	—	*C. jejuni* found in three birds with low antibiotic resistance	(66)
Portugal	Poultry 60% (*n* = 59); swine 59% (*n* = 65); black rats 57% (*n* = 31); sparrows 46% (*n* = 61); ducks 41% (*n* = 21); cows 20% (*n* = 32); sheep 15% (*n* = 27)		Also looked at antimicrobial resistance	(67)
Swine				
Norway	100% (*n* = 114)	—	More than 1,200 wild and domestic mammals were surveyed	(68)
Netherlands	At slaughter (SI contents) 79%; carcasses postslaughter 9%	(4,000 cfu/g) ND	Dry cool conditions thought responsible for rapid *Campylobacter* die-off, while *Salmonella* persisted	(69)
United States	Gilts 76% (*n* = 50); pregnant sows 100% (*n* = 9)		76% *C. jejuni*, 21% *C. coli*, and 3% *C. lari*	(70)
	Newborn piglets 58% (*n* = 73); weaned piglets 100% (*n* = 20)		87% *C. jejuni*, 13% *C. coli*	
Netherlands	Pigs during fattening (feces), 85% (*n* = 7, *n* = 10)	4.1 log N/g	ND	(71–73)
Poultry broilers				
United States	50–100%	4–16,000	Spring has lowest flock positivity	(74)
United Kingdom	Birds 27% (*n* = 12,233)		In 5-year study, 36% of 251 shed flocks infected, but only 9% of shed flocks infected between successive flocks	(75)
Netherlands	Flocks 82% (*n* = 187)		Flock positivity was seasonal, with 100% in June–September and 50% in March	(76)
Dairy herds				
United Kingdom	Feces, 10 of 12 herds positive, 10–72% of test cows	ND	ND	(77)
	4 average size dairy herds	Feces, 70 MPN/gfw (SE = 2, *n* = 1,080)	Spring and autumn peaks, "evidence of true seasonality"	(78)
United States	Feces 38% (*n* = 2,085)	—	Extensive study of farm practice including whether herds consumed chlorinated water, which appears to have no predictive effects	(79)
New Zealand	Feces, summer 24% (*n* = 72); autumn 31% (*n* = 106); winter 12% (*n* = 95)	—	Rectal swabs taken in summer, autumn, and winter, with a fairly even split between *C. jenjuni* and *C. coli*	(80)
Beef cattle				
United Kingdom	At slaughter (SI contents) 89% (*n* = 360)	6.1 × 10² MPN/g (SE = 2; *n* = 1,080)	No significant seasonal periodicity	(78)
United Kingdom	Calves (SI contents), ND	3.3 × 10⁴ MPN/g (SE = 180, *n* = 32)	ND	(78)
Sheep				
Norway	Feces 8%, (*n* = 197)	—	More than 1,200 wild and domestic mammals were surveyed in this study	(68)
United Kingdom	SI contents 92%; feces 30–46%	—	Survived in feces for up to 4 days; shedding is seasonal, peaking with lambing, weaning, and movements to new pasture	(81)
United Kingdom	Lambs at slaughter (SI contents) 92% (*n* = 360)	4 log 10 MPN/gfw (*n* = 1,080, SD = 0.16) to 7 log MPN/gfw	Seasonality evident; time series not indicative of annual peaks	(82)
United Kingdom	Sheep (feces) 29% (*n* = 420)	ND	NF	(82)

Abbreviations: cfu, colony-forming units; gfw, gram fresh weight; MPN, most probable number; ND, not done; NF, significant association not found; SI, small intestine.

processing sectors. Therefore, the number of humans exposed in this way is relatively small in developed countries, and there is some evidence that persons exposed in an occupational setting build up an immunity to these enteric pathogens (*56*). Second, there is evidence that the ecologic filter represented by personal hygiene is very effective (*83*). Even in situations where people are very exposed, such as changing babies's diapers, washing one's hands is likely to remove virtually all pathogens. Where hygiene is poor, as is expected of the very young (under 5 years of age), our disease surveillance information has shown an increased incidence of disease (*1*).

In terms of modeling human exposure to *Campylobacter* through direct and/or indirect contact with feces and to simulate the pathogen survival trajectories, we need to know the following:
• How many *Campylobacter* pathogens are excreted with feces?
• How long do *Campylobacter* survive in feces?
• How many can be transferred onto fingers, skin, fur, or other relevant intermediate environmental vectors?

Table 3. Survival of *Campylobacter* pathogens in aquatic environments and on intermediate environmental vectors outside of animal hosts.

Environmental setting	Positive environmental samples and pathogen load	Seasonality and other notable features	Reference
Finished drinking water environments			
New Zealand	29% ($n = 24$), median MPN < 0.07 100/mL		(*84*)
Greece	1% ($n = 500$)	Occurrence significantly higher when coliform bacteria present, but no difference in frequency of occurrence between chlorinated and nonchlorinated water	(*85*)
Wastewater environments			
Netherlands		Review	(*86*)
United Kingdom			(*87*)
	2–50×10^2/100 mL		
	2.2×10^3/100 mL to 5.1×10^4/100 mL	May–June peak, sewage effluent from abattoir and animal processing plants	(*88*)
	46% of pond samples and 45% of all drain samples were positive	Positive samples year-round; E. coli not indicative of *Campylobacter* presence	(*89*)
Netherlands	80–1,600 MPN/100 mL	Minimum June–August	(*90*)
Italy	630–3,200/100 mL	Maximum May–July	(*91*)
Aquatic environments			
Greece	16% ($n = 86$), < 10/100 mL	Contamination not predicted by the standard indicator bacteria	(*92*)
New Zealand	Rivers 60% ($n = 30$), median MPN 0.18/100 mL		(*84*)
	Shallow ground water 75% ($n = 18$), median MPN 0.12/100 mL		
	Roof water 38% ($n = 24$), median MPN < 0.06/mL		
United States, Washington State	Sampled a number of mountain streams and lakes	Recovery rates highest in fall/winter, lowest in spring and summer	(*93*)
United Kingdom	22% ($n = 49$), 10–230 MPN/100 mL	Coastal and estuary samples	(*94*)
	16% ($n = 44$), 10–36/100 mL	River samples	
	Filtration method 43% ($n = 312$); 21% by MPN (< 10 *Campylobacter*/100 mL)	Autumn and winter peaks; greatest MPN downstream of sewage outfalls; rural and urban samples	(*39*)
	Groundwater spring contamination, isolated from 550-mL and 100-mL filter enrichment	Not isolated in the absence of fecal indicators	(*95*)
United Kingdom, river, canal, estuary		Higher numbers in winter; lower or none in May, June, and July; negative correlation with infection incidence in community	(*38*)
United Kingdom, Morecombe Bay	Seasonal variation in *C. jejuni, C. coli*, UPTC, *C. lari,* with higher numbers found in winter		(*96–98*)
Human skin and hair surfaces			
Fingertips	Suspensions of 10^6–10^7 *C. jejuni* dried on fingertips for 1–4 min	Organisms removed by hand washing with either soap and water or just water and drying hands on paper towels	(*83*)
Food surfaces			
United Kingdom	Grown at 37°C on high-pH meat (pH 6.4), but not on normal pH meat (pH 5.8); population decay rates same for both pHs; very slow decay rate at 1°C for high-pH meat		(*99*)
	Kitchen meat samples 73% ($n = 489$);	83% chicken samples positive; all meats had some positives; *C. jejuni*, 57 sero/phage types	(*100*)
	Chicken giblets 41%, thawed chicken juices 22%, fresh chickens 88% ($n = 34$)	Multiple visits to four large commercial kitchens Internal and external swabs of various meats	(*101*)
Insect vectors			
House flies	Sample of 32 house flies allowed to ingest *C. jejuni*, 20% recovery from feet and ventral surface, 70% recovery from viscera		(*102*)
House flies	Chicken farm 51% ($n = ?$)	Authors suggest that flies may be an important vector between animals	(*103*)
	Piggery 43% ($n = ?$)		
Other			
Beach sand	45% ($n = 182$) and > 30% dry sand samples also contaminated	Presence greater in wet sand, but still 30% of dry sand samples positive	(*104*)
Beach sand	Sediment samples showed no seasonality, unlike water samples taken at the same time; sediment samples had greater numbers of *Campylobacter* than overlying water samples		(*96*)

Abbreviations: ?, unknown; MPN, most probable number; UPTC, urease-positive thermophilic campylobacters.

• How long does at least an infective dose survive on intermediate environmental vectors?
• How often does an infective dose makes it to an oral exposure?

These questions reduce to the following eco-environmental modeling problems: *a*) pathogen survival in feces; *b*) pathogen survival on human hands, fingers, and other intermediate environmental vectors; and *c*) the ecologic filter of personal hygiene (especially important in occupational settings, diaper changing, and among children under 5 years of age).

On the face of it, the pathogen survival trajectories through aquatic environments are more complex and more uncertain than trajectories of direct exposure to feces or through human-to-animal, animal-to-human, human-to-human, or animal-to-animal contact. However, observational studies suggest that waterborne outbreaks are a more important component of the disease ecology than human-to-human spread. We are as yet unable to account for this apparent contradiction, but environmental, behavioral, and possibly immunologic factors (of which the latter is likely to be important in occupational settings of repeated exposure) are the mechanisms which the modeling will explore. However, although less complex trajectories might be more capable of delivering more hazardous exposures to *Campylobacter*, the risk of any particular trajectory must also incorporate the number of possible exposures, which is likely to be much greater with respect to food and water-exposure mechanisms.

There are three major issues: *a*) complexity of the survival trajectories in terms of the environmental constraints and ecologic filters; *b*) uncertainty in terms of the VNC state of *Campylobacter*; and *c*) the variability among strains of *Campylobacter*. Many studies have found *Campylobacter* in aquatic environments; in fact, its recovery is common and widespread [Table 3 (*38,39,83–104*)]. Sewage treatment (*86–91*) and water-treatment processes (*84,85*) are less than perfect ecologic filters. Animal access to drinking water catchments and proximity to rivers would seem to be an important factor in determining exposure through aquatic ecosystems. The role of birds in the survival trajectory of the pathogens may be especially important in the longer-distance movement of *Campylobacter* (Table 2).

The VNC state of *Campylobacter*, also referred to as a coccoid form, introduces additional uncertainty into pathogen survival trajectories through aquatic environments. Uncertainty arises in the interpretation of many observational studies of the disease ecology by increasing the number of false-negative analyses where *Campylobacter* exists but is not found because it is in the VNC state. Additionally, infectivity after recovery of *Campylobacter* in the intestinal tract of animal hosts appears possible, but is not well documented (*105*). Changes in virulence after its recovery may also be possible (*45*),

and the modification of its genotypic structure may be obfuscating attempts to observe flows in the environment (*106*).

Drinking water contaminated with *Campylobacter* pathogens appears to be an efficient exposure mechanism. The degree to which water is regularly contaminated appears to be the largest unknown, but from disease surveillance, small waterborne outbreaks appear to be common. The identification of the ratio of identified to unidentified outbreaks might be a key piece of epidemiologic information that could help resolve the relative proportion of the population regularly being exposed to contaminated water. In terms of modeling the pathogen survival trajectories through aquatic environments, we need to know *a*) how many *Campylobacter* pathogens are entering aquatic environments; *b*) how long they survive in various aquatic environments; *c*) how effective sewage treatment and drinking-water treatment are at removing pathogens from contaminated water; and *d*) how often an infective dose makes it to an oral exposure?

Consequently, there are three primary modeling problems: *a*) survival during the period required to get into an aquatic environment, *b*) survival during the residence time in an aquatic environment, and *c*) the ecologic filters concerning sewage treatment, water treatment, and human behaviors in the use of water. All of the modeling issues associated with the survival of *Campylobacter* in water

Table 4. Environment factors controlling survival of *Campylobacter* pathogens outside of the intestinal tract of host animals.

Factor	Environmental temperature	*Campylobacter* spp.[a]	Comments	Reference
Replication conditions				
Minimum	34–36°C	*C. fetus* spp. *jejuni*, 12 strains	—	(*99*)
	31–32°C	*C. jejuni*, 2 strains	—	(*21,43*)
Optimum	37–42°C	*C. jejuni*, 2 strains	—	(*21*)
Maximum	45°C	*C. jejuni*, 2 strains	—	(*21*)
Survival conditions				
Review papers	Various	Various	—	(*42,107*)
30–65 days	4°C	*C. jejuni*	Isolated from wastewater using various culturing techniques	(*43*)
18–45 days	12°C			
4–7 days	25°C			
2–9 days	20°C and 30°C	*C. coli*, *C. jejuni*	Half-shelled and unopened oysters	
8–14 days	3°C and 10°C		Survival better at 3°C than at 10°C in half-shelled oysters; survival better in bottled oysters at same temperature	
Viable for months	–20°C and –24°C		Frozen half-shelled	(*108*)
18–28 days and 16 weeks to VNC	4°C	*C. jejuni*, 4 strains	VNC recovered for two strains using mice[b]	(*109*)
> 4 months, filtered stream water in lab flask	4°C	*C. jejuni*	Filtered stream water in lab flask; shaking and aeration decrease survivability; increasing temperature decreases recoverability	(*110*)
202 hr (avg)	4°C	*C. jejuni*, 17 strains	Water microcosms and biofilm studies show consistency in survival across *C. jejuni* strains	(*111*)
176 hr (avg)	10°C			
43 hr (avg)	22°C			
22 hr (avg)	37°C			
7 months, laboratory	4°C	*C. jejuni*	Identified viability through respiration	(*105*)
12 hr to nonculturability	37°C in darkness	*C. lari*, *C. jejuni*, *C. coli*	*C. lari* and UPTCs survived longer, survival in sea water	(*98*)
5 days to nonculturability	4°C in darkness		Slightly better than in river water	(*98*)
30–60 min to nonculturability	Not temperature dependent		Exposed to UVB in lab simulating sunny June day	(*98*)

UVB, ultraviolet B radiation.
[a]Spiral forms of thermophilic *Campylobacter* (i.e., *C. jejuni*, *C. coli*, *C. lari*, and *C. upsaliensis*) are gram-negative, oxidase-positive, S-shaped morphology. [b]VNC morphology occurs in response to unfavorable environmental conditions.

appear to indicate that water temperature may be the primary determinant of pathogen longevity [Table 4 (*21,42,43,98,99,105–111*)].

Food preparation and consumption of certain meats, particularly chicken, are identified through observational studies as the greatest risk of campylobacteriosis, despite the number of ecologic filters between source and exposure (Figure 2). From a perspective of pathogen survival, food preparation is the final ecologic filter before human exposure. It appears that food derived from poultry, cattle, and sheep are regularly, if not perpetually, contaminated with *Campylobacter* (Table 2). Animal management and the subsequent slaughtering and food processing represent ecologic filters, but they do not appear to be entirely effective in removing *Campylobacter* from the environment (Table 3). However, these filters may be important both in reducing the pathogen load and in providing identifiable break points for future interventions.

In terms of modeling pathogen survival trajectories through food processing, preparation, and consumption exposures, we need to know *a*) how many *Campylobacter* pathogens are transferred onto foodstuffs destined for human consumption; *b*) how long they survive on food and food preparation surfaces; *c*) how many pathogens can be transferred between these intermediate environmental vectors (e.g., kitchen implements); *d*) how many are transferred between foodstuffs in the process of cross-contamination; *e*) how effective the food-related ecologic filters of food processing and food preparation are; and *f*) how often an infective dose makes it to an oral exposure.

These considerations reduce to the following modeling problems: *a*) survival on food surfaces, *b*) survival during the transfer between intermediate environmental vectors, and *c*) the ecologic filters of food processing, food preparation, and personal and kitchen hygiene.

Discussion

An examination of the literature dealing with the environmental constraints of pathogen survival does not clearly indicate how the *Campylobacter* pathogens are moving through the environment, but only ample evidence of its occurrence. The examination of animals, aquatic environments, and food-related surfaces indicates that there is an abundance of animal reservoirs (Table 2) and a variety of survival trajectories through the environment (Table 3) with rather common environmental survival parameters (Table 4). The ecologic model for campylobacteriosis we propose in this paper (Figure 2, Table 1) is not intended to predict how *Campylobacter* moves through the environment, but will provide a tool to study the dynamics of this system.

The proposed eco-environmental modeling will attempt to do three things. First, it will

assist in bringing together the existing information on the survival of *Campylobacter* in the environment. In this paper, we have labeled the organizing principle "pathogen survival trajectories." This Lagrangian approach seeks to define the relative survival potential for pathogens moving through the environment. Two key aspects define the movement of pathogens outside their animal hosts: a continuous decay in population numbers and movement of a proportion of the population into the VNC state, and passage through ecologic filters, which further reduces the pathogen population size. Although the first component is shaped by environmental factors such as temperature and nutrient availability, the ecologic filters are also defined by a number of factors, including behavioral factors such as personal hygiene or culinary practices.

Second, the proposed eco-environmental modeling provides an alternative perspective on the ecology of this disease. Three types of information shape our current understanding of human campylobacteriosis: human disease surveillance, epidemiologic case–control studies, and microbiologic investigations. Disease surveillance information has shown, for the last decade at least, a high incidence of campylobacteriosis within developed countries and large seasonal swings in the incidence of human disease. However, disease surveillance information is limited by the nature of the surveillance systems. It is generally accepted that the incidence is many times higher than we can observe and that there is no clear explanation for the seasonality. Case–control studies point to food, particularly poultry and undercooked poultry, raw water, and unpasteurized milk, to name a few, as sources of elevated risk. Case–control studies are not infallible, however. Case–control studies rely on recall ability for food and other activities and particularly on the ability of the control group to recall diarrhea events. This is problematic, particularly where controls may have had only minor symptoms or no symptoms. There have been hundreds of microbiologic studies of *Campylobacter* pathogens that have examined survival in a myriad of environments (Tables 2, 3, and 4) (e.g., pathogenesis, virulence, and strain typing). Despite the immense effort, there does not appear to be any overarching structure into which these new pieces of knowledge are being organized. It is difficult to see where this accumulation of knowledge is taking us. The model proposed here operates from a pathogen perspective that would be at home in the microbiologic discipline, but that also allows epidemiologic studies of human and animal disease incidence to be integrated into and evaluated against microbiologic knowledge.

Third, and perhaps most importantly, the proposed ecologic model for campylobacteriosis may provide a tool to help us better

identify what we do not know and to evaluate how important these unknowns are likely to be in the context of the overall ecology. For example, our disease surveillance systems do not provide strong evidence of human-to-human spread. It is difficult to assess the effectiveness of human-to-human contact as an exposure route compared with the relatively more complex trajectories through water and food. A working mathematical model may allow us to replicate enough of the dynamics to assess whether our lack of knowledge is really important in this area. In short, it is a tool that can assist in the building and evaluation of knowledge.

Whether the proposed ecologic model provides a useful alternative perspective on the ecology of campylobacteriosis will be judged in part on the success of this perspective in fostering new insight. Consequently, the ultimate success of the proposed model, beyond whatever conceptual attractiveness the model may hold, will lie in its implementation. Modeling should work symbiotically with empiric research to help guide and evaluate the acquisition of new knowledge, as has been ably demonstrated with the effort of the climate research community to bring these two approaches together (*112*).

REFERENCES AND NOTES

1. Lane L, Baker M. Are we experiencing an epidemic of *Campylobacter* infection? Commun Dis N Z 93(5):57–63 (1993).
2. Anonymous. National Surveillance Data. New Zealand Public Health Rep 8(1):6–7 (2001). Available: http://www.moh.govt.nz/nzphr.html [cited 9 October 2002].
3. Centers for Disease Control and Prevention. Preliminary FoodNet data on the incidence of foodborne illnesses—selected sites, United States, 2000. MMWR Morb Mortal Wkly Rep 50(13):241–246 (2001).
4. Wheeler JG, Sethi D, Cowden JM, Wall PG, Rodrigues LC, Tompkins DS, Hudson MJ, Roderick PJ. Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. Br Med J 318:1046–1050 (1999).
5. Forman RTT, Godron M. Landscape Ecology. New York:John Wiley & Sons, 1986.
6. Aber JD. Terrestrial ecosystems. In: Climate System Modeling (Trenberth KE, ed). Cambridge, UK:Cambridge University Press, 1992;173–200.
7. Corvalán C, Numinen M, Pastides H. Linkage Methods for Environment and Health Analysis: Technical Guidelines. Geneva:World Health Organization, 1997.
8. Blakely TA, Woodward AJ. Ecological effects in multi-level studies. J Epidemiol Community Health 54:367–374 (2000).
9. Rapport DJ, Costanza R, McMichael AJ. Assessing ecosystem health. Trends Ecol Evol 13(10):397–402 (1998).
10. Yassi A, Mas P, Bonet M, Tate RB, Fernandez N, Spiegel J, Perez M. Applying an ecosystem approach to the determinants of health in Centro Habana. Ecosyst Health 5(1):3–19 (1999).
11. Harvey T, Mahaffey KR, Velazquez S, Dourson M. Holistic risk assessment: an emerging process for environmental decisions. Regul Toxicol Pharmacol 22:110–117 (1995).
12. Cole DC, Eyles J, Givson BL, Ross N. Links between humans and ecosystems: the implications of framing for health promotion strategies. Health Promotion Int 14(1):65–72 (1999).
13. Focks DA, Haile DG, Daniels E, Mount GA. Dynamic life table model for *Aedes aegypti* (Diptera: Culicidae): analysis of the literature and model development. J Med Entomol 30(6):1003–1017 (1993).

14. Martin PH, Lefebvre MG. Malaria and climate: sensitivity of malaria potential transmission to climate. Ambio 24(4):200–207 (1995).

15. Martens P. Health and Climate Change: Modeling the Impacts of Global Warming and Ozone Depletion. London:Earthscan Publications Ltd, 1998.

16. Woodward A, Hales A, Weinstein P. Climate change and human health in the Asia Pacific region: who will be most vulnerable? Clim Res 11:31–38 (1998).

17. Weinstein P, Russell N, Woodward A. Drinking water, ecology, and gastroenteritis in New Zealand. Interdisciplinary perspectives on drinking water risk assessment and management (Reichard EG, Hauchmann FS, Sancha AM, eds). IAHS Publication No. 260. Wallingford, Oxfordshire, UK:International Association of Hydrological Sciences, 2000;41–47.

18. Pekkanen J, Pearce N. Environmental epidemiology: challenges and opportunities. Environ Health Perspect 109:1–5 (2001).

19. Anderson RM, May RM. Infectious Diseases of Humans: Dynamics and Control. Oxford, UK:Oxford University Press, 1991.

20. Ketley JM. Pathogenesis of enteric infection by Campylobacter. Microbiology 143:5–21 (1997).

21. Hazeleger WC, Wouters JA, Rombouts FM, Abee T. Physiological activity of Campylobacter jejuni far below the minimal growth temperature. Appl Environ Microbiol 64(10):3917–3922 (1998).

22. Kasabov NK. Foundations of Neural Networks, Fuzzy Systems, and Knowledge Engineering. Cambridge, MA:MIT Press, 1996.

23. Gilks WR, Richardson S, Spieglehalter DJ, eds. Markov Chain Monte Carlo in Practice. Boca Raton, FL:CRC Press, 1996.

24. Vose D. Risk Analysis: A Quantitative Guide, 2nd ed. Chichester, West Sussex, UK:John Wiley & Sons Ltd., 2000.

25. May R. Changing disease in changing environments. In: Health and the Environment (Cartledge B, ed). Oxford, UK:Oxford University Press, 1994; 150–171.

26. José MV, Bobadilla JR. Epidemiological model of diarrhoeal disease and its application in prevention and control. Vaccine 12(2):109–116 (1994).

27. Guerrant RL, Lohr JA, Williams EK. Acute infectious diarrhoea. I. Epidemiology, aetiology and pathogenesis. Pediatr Infect Dis J 5:353–359 (1986).

28. Gatewood LC, Ackerman E, Ewy W, Elveback L, Fox JP. Simulation of models of enteric virus epidemics. Int J Biomed Comput 2:201–213 (1971).

29. Myo A, Maung K, Their U, Bosikov J, Dezelic G, Cvjetanovic B. Epidemiological model of acute bacterial and viral diarrhoeal disease. J Diarrhoeal Dis Res 3:65–72 (1985).

30. Altekruse SF, Sterm NJ, Fields PL, Swerdlow DL. Campylobacter jejuni—an emerging foodborne pathogen. Emerg Infect Dis 5(1):28–35 (1999).

31. Oosterom J, Den Uijl CH, Banffer JRJ, Huisman J. Epidemiological investigation on Campylobacter jejuni in households with a primary infection. J Hyg Camb 92:325–332 (1984).

32. Harris NV, Weiss NS, Nolan CM. The role of poultry and meats in the etiology of Campylobacter jejuni/coli enteritis. Am J Public Health 76:407–411 (1986).

33. Deming MS, Tauxe RV, Blake PA, Dixon SE, Fowler BS, Jones TS, Lockamy EA, Patton CM, Sikes RO. Campylobacter enteritis at a university: transmission from eating chicken and from cats. Am J Epidemiol 126:526–534 (1987).

34. Notermans S, Hoogenboom-Verdegaal A. Existing and emerging foodborne diseases. Int J Food Microbiol 15:197–205 (1992).

35. Eberhart-Phillips JN, Walker N, Garrett N, Bell D, Sinclair D, Rainger W, Bates M. Campylobacteriosis in New Zealand: results of a case-control study. J Epidemiol Community Health 51:686–691 (1997).

36. Palmer SR. Personal communication.

37. Butzler JP, Oosterom J. Campylobacter: pathogenicity and significance in foods. Int J Food Microbiol 12(1):1–8 (1991).

38. Pearson AD, Greenwood MH, Healing TD, Rollins D, Shahamat M, Donaldson J, Colwell RR. Colonization of broiler chickens by waterborne Campylobacter jejuni. Appl Environ Microbiol 59(4):987–996 (1993).

39. Jones K, Betaieb M, Telford DR. Thermophilic campylobacters in surface waters around Lancaster, UK:

40. Bolton FJ, Coates D, Hutchinson DN, Godfree AF. A study of thermophilic campylobacters in a river system. J Appl Bacteriol 62:167–176 (1987).

41. Mann DR, Akinbami MA, Gould KG, Ansari AA. Seasonal variations in cytokine expression and cell-mediated immunity in male rhesus monkeys. Cell Immunol 200(2):105–115 (2000).

42. Thomas C, Gibson H, Hill DJ, Mabey M. Campylobacter epidemiology: an aquatic perspective. J Appl Microbiol 85:168S–177S (1999).

43. Hazeleger WC, Janse JD, Koenraad PMFJ, Beumer RR, Rombouts FM, Abee T. Temperature-dependent membrane fatty acid and cell physiology changes in coccoid forms of Campylobacter jejuni. Appl Environ Microbiol 61:2713–2719 (1995).

44. Tholozan JL, Capperlier JM, Tissier JP, Gelattre G, Federighi M. Physiological characterization of viable-but-nonculturable Campylobacter jejuni cells. Appl Environ Microbiol 65(3):1110–1116 (1999).

45. Talibart R, Denis M, Castillo A, Cappelier JM, Ermel G. Survival and recovery of viable but nonculturable forms of Campylobacter in aqueous microcosm. Int J Food Microbiol 55(1–3):263–267 (2000).

46. Black RE, Levine MM, Clements ML, Highs TP, Blaser MJ. Experimental C. jejuni infection in humans. J Infect Dis 157:472–479 (1988).

47. Black RE, Perlman D, Clements ML, Levine MM, Blaser MJ. Human volunteer studies with Campylobacter jejuni. In: Campylobacter jejuni: Current Status and Future Trends (Nachamin I, Blaser MJ, Tompkins LS. eds), Washington, DC:American Society of Microbiology, 1992;201–215.

48. Medema GJ, Teunis PFM, Havelaar AH, Haas CN. Assessment of the dose-response relationship of Campylobacter jejuni. Int J Food Microbiol 30:101–111 (1996).

49. Teunis P, Havelaar A, Vliegenthart J, Roessink G. Risk assessment of Campylobacter species in shellfish: identifying the unknown. Water Sci Technol 35(11–12):29–34 (1997).

50. Morgan D, Gunneberg C, Gunnell D, Healing TD, Lamerton S, Soltanpoor N, Lewis DA, White DG. An outbreak of Campylobacter infection associated with the consumption of unpasteurised milk at a large festival in England. Eur J Epidemiol 10:581–585 (1994).

51. Riordan T, Humphrey TJ, Fowles A. A point source outbreak of Campylobacter infection related to bird-pecked milk. Epidemiol Infect 110:261–266 (1993).

52. Sacks JJ, Lief S, Baldy LM, Berta S, Patton CM, White MC, Bigler WJ, White JJ. Epidemic campylobacteriosis associated with a community water supply. Am J Public Health 76:424–429 (1986).

53. Melby K, Gondrosen B, Gregusson S, Ribe H, Dahl PP. Waterborne campylobacteriosis in northern Norway. Int J Food Microbiol 12:151–156 (1991).

54. Millson M, Bokhout M, Carlson J, Spielberg L, Akdusm R, Borczyk A, Lior H. An outbreak of Campylobacter jejuni gastro-enteritis linked to meltwater contamination of a municipal well. Can J Public Health 82:27–31 (1991).

55. Jones KM, Harrop C. A study of Campylobacter enteritis. J Int Med Res 91(1):40–43 (1981).

56. Cawthraw SA, Lind L, Kaijser B, Newell DG. Antibodies, directed towards Campylobacter jejuni antigens, in sera from poultry abattoir workers. Clin Exp Immunol 122(1):55–60 (2000).

57. Fernández H, Kahler K, Salazar R, Ríos MA. Prevalence of thermotolerant species of Campylobacter and their biotypes in children and domestic birds and dogs in southern Chile. Rev Inst Med Trop Sao Paulo 36(5):433–436 (1994).

58. Yogasundram K, Shane SM, Harrington KS. Prevalence of Campylobacter jejuni in selected domestic and wild birds in Louisiana. Avian Dis 33:664–667 (1989).

59. Blaser M, Cravens J, Powers BW, Wang WL. Campylobacter enteritis associated with canine infection. Lancet 2(8097):979–981 (1978).

60. Blaser M, LaForce F, Wilson NA, Wang WL. Reservoirs for human campylobacteriosis. J Infect Dis 141:665–669 (1980).

61. Kapperud G, Rosef O. Avian wildlife reservoir of Campylobacter fetus subsp. jejuni, Yersinia spp., and Salmonella spp. in Norway. Appl Environ Microbiol 45(2):375–380 (1983).

62. Luechtefeld NA, Blaser MJ, Reller LB, Wang WL.

63. Isolation of Campylobacter fetus subsp. jejuni from migratory waterfowl. J Clin Microbiol 12:406–408 (1980).

64. Ito K, Kubokura Y, Kaneko K, Totake Y, Ogawa M. Occurrence of Campylobacter jejuni in free-living wild birds from Japan. J Wildl Dis 24:467–470 (1988).

65. Maruyama S, Tanaka T, Katsube Y, Nakanishi H, Nukina M. Prevalence of thermophilic campylobacters in crows (Corvelevaillantii, Corvus corone) and serogroups of the isolates. Nippon Juigaku Zasshi 52(6):1237–1244 (1990).

66. Pacha RE, Clark GW, Williams EA, Carter AM. Migratory birds of central Washington as reservoirs of Campylobacter jejuni. Can J Microbiol 34(1):80–82 (1988).

67. Palmgren H, Selling M, Bergström S, Olsen B. Enteropathogenic bacteria in migrating birds arriving in Sweden. Scand J Infect Dis 29:565–568 (1997).

68. Cabrita J, Rodrigues J, Braganca F, Morgado C, Pires I, Penha Goncalves A. Prevalence, biotypes, plasmid profile and antimicrobial resistance of Campylobacter isolated from wild and domestic animals from northeast Portugal. J Appl Bacteriol 73:279–285 (1992).

69. Rosef O, Gondrosen B, Kapperud G, Underdal B. Isolation and characterization of Campylobacter jejuni and Campylobacter coli from domestic and wild mammals in Norway. Appl Environ Microbiol 46:855–859 (1983).

70. Oosterom J, Dekker R, de Wilde GJA, van Kempen-de Troye F, Engels GB. Prevalence of Campylobacter jejuni and Salmonella during pig slaughtering. Vet Q 7(1):31–34 (1985).

71. Young CR, Harvey R, Anderson R, Nisbet D, Stanker LH. Enteric colonisation following natural exposure to Campylobacter in pigs. Res Vet Sci 68(1):75–78 (2000).

72. Weijtens MJ, Bijker PG, Van der Plas J, Urlings HA, Biesheuvel MH. Prevalence of Campylobacter in pigs during fattening: an epidemiological study. Vet Q 15(4):138–143 (1993).

73. Weijtens MJ, Van der Plas J, Bijker PG, Urlings HA, Koster D, van Logtestijn JG, Huis in't Veld JH. The transmission of Campylobacter in piggeries; an epidemiological study. J Appl Microbiol 83(6):693–698 (1997).

74. Weijtens MJ, Reinders RD, Urlings HA, Van der Plas J. Campylobacter infections in fattening pigs; excretion pattern and genetic diversity. J Appl Microbiol 86(1):63–70 (1999).

75. Stern NJ. Influence of season and refrigerated storage on Campylobacter spp. contamination of broiler carcasses. J Appl Poult Res 4:235–238 (1995).

76. Pearson AD, Greenwood MH, Feltham RKA, Healing TD, Donaldson J, Jones DM, Colwell RR. Microbial ecology of Campylobacter jejuni in a United Kingdom chick supply chain: intermittent common source, vertical transmission and amplification by flock propagation. Appl Environ Microbiol 62(12):4614–4620 (1996).

77. Jacobs-Reitsma WF, Bolder NM, Mulder RWAW. Cecal carriage of Campylobacter and Salmonella in Dutch broiler flocks at slaughter: a one year study. Poult Sci 73:1260–1266 (1994).

78. Humphrey TJ, Beckett P. Campylobacter jejuni in dairy cows and raw milk. Epidemiol Infect 98(3):263–269 (1987).

79. Stanley KN, Wallace JS, Currie JE, Diggle PJ, Jones K. The seasonal variation of thermophilic campylobacters in beef cattle, dairy cattle and calves. J Appl Microbiol 85:472–480 (1998).

80. Wesley IV, Wells SJ, Harmon KM, Green A, Schroeder-Tucker L, Glover M, Siddique I. Fecal shedding of Campylobacter and Arcobacter spp. in dairy cattle. Appl Environ Microbiol 66(5):1994–2000 (2000).

81. Meanger JD, Marshall RB. Seasonal prevalence of thermophilic Campylobacter infections in dairy cattle and a study of infection of sheep. N Z Vet J 37:18–20 (1989).

82. Jones K, Howard S, Wallace JS. Intermittent shedding of thermophilic campylobacters by sheep at pasture. J Appl Microbiol 86(3):531–536 (1999).

83. Stanley KN, Wallace JS, Currie JE, Diggle PJ, Jones K. Seasonal variation of thermophilic campylobacters in lambs at slaughter. J Appl Microbiol 84(6):1111–1116 (1998).

84. Coates D, Hutchinson DN, Bolton FJ. Survival of thermophilic campylobacters on fingertips and their elimination by washing and disinfection. Epidemiol Infect 99(2):265–274 (1987).

85. Savill MG, Hudson JA, Ball A, Klena JD, Scholes P, Whyte RJ, McCormick RE, Jankovic D. Enumerating of Campylobacter in New Zealand recreational and drinking waters. J Appl Microbiol 91:38–46 (2001).

85. Arvanitidou M, Stathoppoulos GA, Katsouyannopoulos VC. Isolation of *Campylobacter* and *Yersinia* spp. from drinking waters. J Travel Med 1(3):156–159 (1994).

86. Koenraad PMFJ, Rombouts FM, Notermans SHW. Epidemiological aspects of thermophilic *Campylobacter* in water-related environments: a review. Water Environ Res 69(1):52–63 (1997).

87. Jones K, Betaieb M, Telford DR. Seasonal variation of thermophilic campylobacters in sewage sludge. J Appl Bacteriol 69(2):185–189 (1990).

88. Jones K, Betaieb M, Telford DR. Correlation between environmental monitoring of thermophilic campylobacters in sewage effluent and the incidence of *Campylobacter* infection in the community. J Appl Bacteriol 69(2):235–240 (1990).

89. Mawer SL. Campylobacters in man and the environment in Hull and East Yorkshire. Epidemiol Infect 101:287–294 (1988).

90. Koenraad PMFJ, Hazeleger WC, Van der Laan T, Beumer RR, Rombouts FM. Survey of *Campylobacter* spp. in sewage plants in the Netherlands. Food Microbiol 11:65–73 (1994).

91. Stampi S, De Varoli O, de Luca G, Zanetti F. Occurrence, removal and seasonal variation of 'thermophilic' campylobacters in a sewage treatment plant in Italy. Zentralbl Hyg Umweltmed 193(3):199–210 (1992).

92. Arvanitidou M, Stathopoulos GA, Constantinidis TC, Katsouyannopoulos V. The occurrence of *Salmonella*, *Campylobacter* and *Yersinia* spp. in river and lake waters. Microbiol Res 150:153–158 (1995).

93. Carter JM, Pacha RE, Clark GW, Williams EA. Seasonal occurrence of *Campylobacter* spp. in surface waters and their correlation with standard indicator bacteria. Appl Environ Microbiol 53:523–526 (1987).

94. Bolton FJ, Hinchcliffe PM, Coates D, Robertson L. A most probable number method for estimating small numbers of campylobacters in water. J Hyg (Lond) 89(2):185–190 (1982).

95. Stanley K, Cunningham R, Jones K. Isolation of *Campylobacter jejuni* from groundwater. J Appl Microbiol 85(1):187–191 (1998).

96. Obiri-Danso K, Jones K. Distribution and seasonality of microbial indicators and thermophilic campylobacters in two freshwater bathing sites on the River Lune in northwest England. J Appl Microbiol 87(6):822–832 (1999).

97. Obiri-Danso K, Jones K. The effect of a new sewage treatment plant on faecal indicator numbers, campylobacters and bathing water compliance in Morecombe Bay. J Appl Microbiol 86(4):603–614 (1999).

98. Obiri-Danso K, Paul N, Jones K. The effects of UVB and temperature on the survival of natural populations and pure cultures of *Campylobacter jejuni*, *Camp. coli*, *Camp. lari* and urease-positive thermophilic campylobacters (UPTC) in surface waters. J Appl Microbiol 90(2):256–267 (2001).

99. Gill CO, Harris LM. Survival and growth of *Campylobacter fetus* subsp. *jejuni* on meat and in cooked foods. Appl Environ Microbiol 44(2):259–263 (1982).

100. Kramer JM, Frost JA, Bolton FJ, Wareing DR. *Campylobacter* contamination of raw meat and poultry at retail sale: identification of multiple types and comparison with isolates from human infection. J Food Prot 63(12):1654–1659 (2000).

101. Dawkins HC, Bolton FJ, Hutchinson DN. A study of the spread of *Campylobacter jejuni* in four large kitchens. J Hyg (Lond) 92(3):357–364 (1984).

102. Shane SM, Montrose MS, Harrington KS. Transmission of *Campylobacter* jejuni by the housefly (*Musca domestica*). Avian Dis 29(2):384–391 (1985).

103. Rosef O, Kapperud G. House flies (*Musca domestica*) as possible vectors of *Campylobacter fetus* subsp. *jejuni*. Appl Environ Microbiol 45(2):381–383 (1983).

104. Bolton FJ, Surman SB, Martin K, Wareing DR, Humphrey TJ. Presence of *Campylobacter* and *Salmonella* in sand from bathing beaches. Epidemiol Infect 122(1):7–13 (1999).

105. Làzaro B, Carcamo J, Audicana A, Perales I, Fernandez-Astorga A. Viability and DNA maintenance in nonculturable spiral *Campylobacter jejuni* cells long-term exposure to low temperatures. Appl Environ Microbiol 65(10):4677–4681 (1999).

106. Hänninen M-L, Hakkinen M, Rautelin H. Stability of related human and chicken *Campylobacter jejuni* genotypes after passage through chick intestine studied by pulsed-field gel electrophoresis. Appl Environ Microbiol 65(5):2272–2275 (1999).

107. Thomas C, Hill DJ, Mabey M. Evaluation of the effect of temperature and nutrients on the survival of *Campylobacter* spp. in water microcosms. J Appl Microbiol 86(6):1024–1032 (1999).

108. Arumugaswamy RK, Proudford RW, Eyles MJ. The response of *Campylobacter jejuni* and *Campylobacter coli* in the Sydney rock oyster (*Crassostrea commercialis*), during depuration and storage. Int J Food Microbiol 7(3):173–183 (1988).

109. Jones K, Sutcliffe EM, Curry A. Recovery of viable but non-culturable *Campylobacter jejuni*. J Gen Microbiol 137:2477–2482 (1991).

110. Rollins DM, Colwell RR. Viable but nonculturable stage of *Campylobacter jejuni* and its role in survival in the natural aquatic environment. Appl Environ Microbiol 52:531–538 (1986).

111. Buswell CM, Herlihy YM, Lawrence LM, McGuiggan JTM, Marsh PD, Keevil CW, Leach SA. Extended survival and persistence of *Campylobacter* spp. in water and aquatic biofilms and their detection by immunofluorescent-antibody and –rRNA staining. Appl Environ Microbiol 64(2):733–741 (1998).

112. Houghton JT, Meira Filho LG, Callander BA, Harris N, Kattenberg A, Maskell K, eds. 1996. Climate Change 1995: The Science of Climate Change. Cambridge, UK:Cambridge University Press, 1996.