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Acute illness from *Campylobacter jejuni* may require high doses while infection occurs at low doses

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ABSTRACT

Data from a set of different studies on the infectivity and pathogenicity of *Campylobacter jejuni* were analyzed with a multilevel model, allowing for effects of host species (nonhuman primates and humans) and different strains of the pathogen.

All challenge studies involved high doses of the pathogen, resulting in all exposed subjects to become infected. In only one study a dose response effect (increasing trend with dose) for infection was observed. High susceptibility to infection with *C. jejuni* was found in a joint analysis of outbreaks and challenge studies. For that reason four outbreaks, associated with raw milk consumption, were also included in the present study.

The high doses used for inoculation did not cause all infected subjects to develop acute enteric symptoms. The observed outcomes are consistent with a dose response effect for acute symptoms among infected subjects: a conditional illness dose response relation. Nonhuman primates and human volunteers did not appear to have different susceptibilities for developing enteric symptoms, but exposure in outbreaks (raw milk) did lead to a higher probability of symptomatic campylobacteriosis.

1. Introduction

Campylobacter jejuni is an important foodborne pathogen causing a substantial illness burden worldwide (WHO, 2015). Despite the frequent occurrence of campylobacteriosis, there likely is an even greater number of infections that remain without symptoms (Scallan, 2007; Teunis et al., 2012, 2013). To better understand foodborne transmission of *Campylobacter*, the relation between the magnitude of foodborne exposure and the resulting probabilities of infection and illness must be characterized. Dose response models for *Campylobacter jejuni* infection have been published (Teunis and Havelaar, 2000; Teunis et al., 2005). These analyses were based on a single clinical study in human volunteers (Black et al., 1988), using a single strain of the pathogen (A3249). Use of data from the same experiment to assess a dose response for acute symptoms of *Campylobacter* enteritis predicted the counter-intuitive result of decreasing illness risk with increasing dose (Teunis et al., 1999). Although an explanation was provided, this may also have been caused by inadequate control for immune status of the challenged volunteers. A more recent study included data from two outbreaks caused by consumption of raw milk. Joint analysis with the clinical study data showed that the infectivity of *C. jejuni* may be higher than previously estimated, and also the susceptibility to enteric symptoms was higher in the outbreaks Teunis et al. (2005), and clearly increased with dose. The difference in illness risk may be due to host factors: the clinical study population were adults, likely had partial immunity due to prior exposure, while the outbreak occurred in children, who were much less likely to have had pre-existing immunity.

The dose response relation for infection has been shown to strongly depend on pathogen strain for other pathogens (Teunis et al., 2002a) and for *Campylobacter* (Chen et al., 2006). Therefore it is necessary to extend the existing models to include a greater diversity of strains, to study how much variation in infectivity this would produce. Also, when proceeding from infection to the more distal endpoint of (acute) illness, one would like to include not only strain variation, but also variation in hosts, possibly with different levels of immunity, acquired or innate (Teunis et al., 2002b).

Before attempting to develop models for describing such host effects by covariates as markers of susceptibility (or immunity), it is useful to define baseline information, for establishing the dose response for infection and illness. To that end, we have collected published studies, on

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human challenge with *C. jejuni*, augmented with challenge studies in non-human primates, and outbreaks suitable for analysis as natural challenge events (Brooke et al., 2015; Teunis and Figueras, 2016), and developed a meta-analysis model to study the variation in dose response by strain and host effects.

2. Literature data

The collected data comprise three groups of studies:

1. *Controlled human infection model* (Human challenge studies, 4 papers). These comprise the classical study by Black et al. (1988) reporting challenge experiments with two different strains (A3249 and 81-176); Tribble et al. (2010) that used one of the strains (81-176) from Black et al. (1988) in another challenge experiment, aimed at studying how long immunity lasts, and another study Tribble et al. (2009) reporting on a different strain (CG8421). And finally Kirkpatrick et al. (2013) who again used CG8421 in a study to establish immunity upon homologous rechallenge. Note how most doses were chosen quite high, leading to few non-infections. We also include two additional challenge studies that have not been published, again using CG8421 at slightly lower doses (Table 1).
2. *Outbreaks* (4 papers). The present analysis extends an earlier study (Teunis et al., 2005), that identified two outbreaks both involving raw milk contaminated with *C. jejuni* and a dose response relation between milk consumption and attack rates. One outbreak occurred in the United Kingdom (Evans et al., 1996), the other in the Netherlands (van den Brandhof, 2003). A third study (Korlath et al., 1985) was found, of an outbreak also caused by raw milk in school children, again with a dose response relation between milk consumption and occurrence of acute campylobacteriosis. In this third outbreak the infecting strain was identified as 81-176. A fourth outbreak (Blaser et al., 1987) also reported a dose response relation for acute campylobacteriosis from raw milk, consumed by fraternity pledges. This paper reported responses (numbers infected and with acute symptoms) for subjects who were chronically exposed to raw milk, and those who had not previously consumed raw milk. None of the chronically exposed subjects became infected (or ill). For the present study we only included those that had not been previously exposed, to maintain comparability among outbreak populations. It may be noted that yet another paper was found, reporting a similar outbreak, but there the dose response relation between milk consumption and attack rates was not reported explicitly (Potter et al., 1983). Note that in three outbreaks the *Campylobacter* strains were unknown. The concentration of the pathogens in the contaminated milk was not determined in any of the outbreak studies. In the Blaser et al. (1987) outbreak numbers infected were reported, including asymptomatic infections. In the remaining outbreaks this information was missing too: only acute campylobacteriosis was reported (Table 2).
3. *Challenge studies in non-human primates* (5 papers). To add alternative host species to the analysis, challenge studies of *C. jejuni* in non-human primates were used. Three studies reported challenge of *Macaca mulatta*, Rhesus monkeys (Fitzgeorge et al., 1981; Russell et al., 1993; Islam et al., 2006). In another study *Macaca nemestrina* were challenged with *C. jejuni* (Russell et al., 1989) and in a fifth study the new world monkey species *Aotus nancymae* were challenged (Jones et al., 2006). Note that here, too doses were chosen very high, leading to all exposed animals being infected (Table 3).

Table 1
Data used for (meta-)analysis of the dose response relations for infection and illness of *Campylobacter jejuni*. Data source (publication), strain tested, and host species are listed for each experiment. Also shown: dose, numbers exposed (challenged), numbers infected (shedding or seroconverting) and numbers with symptoms of acute campylobacteriosis.

Reference	Strain	Host	Dose	Exposed	Infected	Symptoms
Black et al. (1988)	A3249	Human	8×10^2	10	5	1
			8×10^3	10	6	1
			9×10^4	13	11	6
			8×10^5	11	8	1
			1×10^6	19	15	2
			1×10^8	5	5	0
			1×10^8	4[a]	4[a]	2[a]
Black et al. (1988)	81-176	Human	1×10^6	7	7	3
			1×10^8	10	10	6
			2×10^9	22	22	9
Tribble et al. (2009)	CG8421	Human	0.97×10^6	8	8	8
			0.84×10^5	7	7	6
			0.54×10^5	8	8	8
Tribble et al. (2010)	81-176	Human	1×10^5	5	5	3
			1×10^7	5	5	2
			1×10^9	36	36	33
			1×10^9	8[b]	6[b]	0[b]
			1×10^9	7[b]	7[b]	4[b]
Kirkpatrick et al. (2013)	CG8421	Human	5×10^5	15	15	14
			5×10^5	8[b]	8[b]	8[b]
Unpublished[c]	CG8421	Human	1.90×10^4	6	6	2
			2.00×10^4	7	7	5
			1.40×10^5	4	4	2
Unpublished[d]	CG8421	Human	1.80×10^5	13	13	11

[a] Bicarbonate buffer instead of milk (not included in analysis).
[b] Rechallenge experiments (short term and long term, not included).
[c] Control group in vaccine (ACE393) challenge study.
[d] Control group in chemoprofylaxis (rifaximin) study.

Table 2
Data used for (meta-)analysis of the dose response relations for infection and illness of *Campylobacter jejuni*. Data source (publication), strain tested, and host species are listed for each experiment. Also shown: dose, numbers exposed (challenged), numbers infected (shedding or seroconverting) and numbers with symptoms of acute campylobacteriosis.

Reference	Strain	Host	Dose	Exposed	Infected	Symptoms
van den Brandhof (2003)	NA[a]	Human	0[b]	35	NA	2
			1/6[b]	12	NA	2
			0.5[b]	18	NA	7
			1[b]	21	NA	13
			2[b]	6	NA	6
Evans et al. (1996)	NA[a]	Human	0[b]	17	NA	2
			0.5[b]	7	NA	3
			1[b]	21	NA	14
			2[b]	5	NA	4
Korlath et al. (1985)	81-176	Human	0[b]	20	NA	0
			1[b]	20	NA	7
			≥ 2[b]	30	NA	18
Blaser et al. (1987)	NA[a]	Human	0[b]	2	0	0
			1[b]	11	8	6
			2[b]	6	6	5
			≥ 3[b]	8	8	8
			1[b]	2[c]	0	0
			2[b]	1[c]	0	0
			≥ 3[b]	1[c]	0	0

[a] Outbreak strains, not identified.
[b] Dose in cups (188 ml) of milk.
[c] In the Blaser et al. (1987) outbreak, these subjects had previously consumed raw milk.