A systematic review and meta-analysis on the incubation period of Campylobacteriosis

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A systematic review and meta-analysis on the incubation period of Campylobacteriosis

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Abstract

Accurate knowledge of pathogen incubation period is essential to inform public health policies and implement interventions that contribute to the reduction of burden of disease. The incubation period distribution of campylobacteriosis is currently unknown with several sources reporting different times. Variation in the distribution could be expected due to host, transmission vehicle, and organism characteristics, however, the extent of this variation and influencing factors are unclear.

The authors have undertaken a systematic review of published literature of outbreak studies with well-defined point source exposures and human experimental studies to estimate the distribution of incubation period and also identify and explain the variation in the distribution between studies. We tested for heterogeneity using I^2 and Kolmogorov Smirnov tests, regressed incubation period against possible explanatory factors, and used hierarchical clustering analysis to define subgroups of studies without evidence of heterogeneity.

The mean incubation period of subgroups ranged from 2.5 to 4.3 days. We observed variation in the distribution of incubation period between studies that was not due to chance. A significant association between the mean incubation period and age distribution was observed with outbreaks involving only children reporting an incubation of 1.29 days longer when compared with outbreaks involving other age groups.

Introduction

Campylobacteriosis is a zoonotic infection caused by a non-spore-forming Gram negative bacteria [1]. The most common species reported in human diseases are *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli* (*C. coli*) [2]. In humans, the main route of transmission of *Campylobacter* is foodborne. Infection occurs following ingestion of undercooked meat and meat products as well as raw or contaminated milk and milk products. Infection can also follow contact with contaminated animals. Person-to-person transmission is rare but can happen. Abdominal cramps and diarrhoea are the most commonly reported symptoms. Non-specific symptoms that can also occur include headache, chills, fever and muscle pain. The duration of illness is usually about a week, with the severity declining after 24 to 48 hours, however 20% of cases may have a relapse[3,4].

According to the World Health Organization (WHO), *Campylobacter sp.* caused 96 million cases of foodborne illness worldwide in 2010 [5]. It is the most commonly reported zoonosis in the European Union accounting for 45.2 cases per 100,000 people [6,7]. In the United Kingdom, there are approximately 9.3 undiagnosed cases in the community for every case reported to the national surveillance system [8], and an estimated 280,000 cases reported each year resulting in over 100 deaths [1,9].

A large proportion of reported cases are sporadic, however, outbreaks of campylobacteriosis have been reported with foodborne [10,11] and non-foodborne [12,13] sources identified. In the UK, 114 outbreaks were reported between 1992 and 2009, affecting a total of 2676 [14]. Outbreak investigation contributes to the reduction of the burden of disease by identifying the source of infection and informing public health strategies and policies. An effective outbreak investigation requires understanding of certain parameters of the infecting pathogen such as the expected incubation period distribution.

Incubation period, which is the time between infection and onset of clinical symptoms, is also important for surveillance and implementation of appropriate public health interventions. In

epidemiological studies, incubation period can be used to estimate the period of exposure, identify and exclude travel related cases, distinguish secondary cases and formulate a hypothesis [15]. It can help in diagnosing possible cases in the absence of microbiological diagnosis [16] and also offers insights into clinical and public health practices [15]. Essential to an outbreak investigation is constructing a case definition where a time restriction, sometimes based on the incubation period, is set to correctly classify cases as being part of the outbreak under investigation [17].

As a result of certain factors such as infectious dose, host factors and possibly, food matrix, the incubation period may vary between individuals. These, among other factors result in a distribution of incubation period. The incubation period distribution of campylobacteriosis is not clearly defined with different times being reported. The National Health Service in England and WHO report two to five days [18,19] while the Public Health Agency of Canada report one to ten days [20]. Incorrect estimations may result in formulating inaccurate case definitions, wrongly defined exposure times, excluding outbreak cases as sporadic or travel related cases and vice versa [21] and misclassifying cases. It is therefore important to correctly estimate the incubation period distribution of campylobacteriosis to support effective outbreak investigations.

Point source outbreaks and human experimental studies, in which healthy volunteers are infected with *Campylobacter* in order to study certain characteristics of the organism, provide an avenue to study the distribution of incubation period. Outbreaks are natural experiments and the outcome can be dependent on the effect of influencing factors, whereas, experimental studies occur in a controlled environment, with less unknown variation as a predetermined dose is administered, and characteristics of participants are screened to ensure similarities.

This study systematically reviewed literature for outbreaks with well-defined point source exposures and human experimental studies. Reported individual patient incubation periods and summary estimates of the distribution of incubation period were extracted and analysed with the aim of describing the distribution of incubation period, identifying any variation in the

distribution between outbreaks above expectation by chance, and attempting to explain any variation identified.

Methods

Research Questions and modified PICO elements

Our research questions were:

1. What is the distribution of incubation period and the average (mean and median) incubation period of *Campylobacter* in humans?
2. Is there heterogeneity between the reported incubations times amongst studies?
    a. Can any observed variation be explained?
    b. What factors are affecting the distribution of incubation periods?

Population studied/Participants -	Laboratory confirmed cases of *Campylobacter spp.* that form part of an outbreak or experimental infection. Probable cases of campylobacter based on clinical symptoms and case definitions in the context of outbreaks
Infectious agent -	*Campylobacter spp.* (all subspecies included)
Route of Infection -	Foodborne and non-foodborne
Outcome -	Onset of gastroenteritis as described or defined by the authors (diarrhoea, vomiting, nausea, abdominal cramps etc.)

Search strategy and selection process

A systematic literature search for peer reviewed publications of observational studies and experimental studies reporting incubation period was carried out on PubMed, Google Scholar and ISI Web of Knowledge. We searched for the following words: "*Campylobacter*", "outbreaks", "experimental", and "humans", combining common variations of the words to create search strings (Appendix 1). The reference lists of identified review papers were also screened to find other relevant studies where incubation period of *Campylobacter spp.* may have been reported. The search was carried out between 21 January to 17 March 2016 and

there was no restriction on the dates of articles returned or on the reported species. Articles in languages other than English were excluded.

Each article went through the selection and/or assessment stage which was done in the following phases:

1) Screening of titles and abstracts for articles with human campylobacteriosis
2) Screening of full text for reporting of incubation period data
3) Review of full text to assess quality of incubation period data reported.
4) Further review of full text to assess exposure times and identify outbreaks with confirmed point source exposures.

The quality assessment undertaken in our review focused on assessing the quality of the incubation period data reported based on a set of criteria developed by one of us (JIH) and not the quality of the overall study. This was done because many of the studies did not necessarily set out to study incubation period, but rather to report on the process of an outbreak investigation or provide evidence on the source of infection in an outbreak. This method of quality assessment enabled us to effectively evaluate the quality of incubation period data reported and the accuracy of the estimation. The set of criteria and corresponding components are listed in Table 1 and a scoring system was used to assess the reported data. Two reviewers were involved in the quality assessment stage, and where there was a difference in opinions, discussions were held until a consensus was reached.

Data extraction

Data was extracted from the studies using a pre-determined format (Table 2). General information on the published article, the study characteristics, as well as specific information on the outbreak or experiment, including attack rate and exposure, pathogen and patient characteristics which might influence incubation time, were extracted from each study according to a predetermined format. The outcome information to be measured was quantitative which was available as summary or raw data. All studies reported at least one summary statistic of the incubation period distribution as a mean, median, mode or range.

The unit of measurement was in days, and where this was reported in hours, we converted to days.

Some studies reported raw incubation period for individual cases either as an epidemic curve or a summary table. Where an epidemic curve was provided, the raw incubation period data was extracted using WebPlotDigitizer version 3.10, which is a free web-based data extraction tool [22]. If a summary table was provided instead, the raw data was also extracted. Where both summary and raw data was provided, the raw data was used for analysis.

Descriptive analyses

Frequencies and percentages were calculated to summarise all studies according to the characteristics identified including: study design (observational or experimental), study type (cohort or case-control study), year of study, *Campylobacter* species, setting of outbreaks, age description of cases, mode of transmission and food vehicle, where applicable.

Using the extracted raw incubation data, histograms of reported incubation periods of individual cases were plotted to re-create the epidemic curves of the outbreaks. All epidemic curves were plotted using a uniform x-axis indicating the incubation period from zero to fifteen days and above, and an individual y-axis indicating the number of cases involved in each outbreak which varied according to the graph.

Statistical analyses

The raw incubation period distributions extracted from relevant studies were used to test for heterogeneity in the reported data and describe the pattern of heterogeneity, while the summary statistics calculated from these and extracted summary statistics for outbreaks without individual patient data were used to identify factors that may explain heterogeneity.

Statistical analyses were carried out using statistical software R version 3.2.3 (2015-12-10) – “Wooden Christmas Tree” [23].

- **Testing for heterogeneity**

We tested for heterogeneity across studies by deriving the value of I^2. A p-value of less than 0.05 from the chi-square test provided statistical evidence of heterogeneity and using the Cochran suggested threshold [24] we interpreted the value of I^2 to determine the magnitude of heterogeneity.

We also performed a two sample Kolmogorov-Smirnov test (KS test) to compare the cumulative distributions between the studies. We applied a bootstrapped version of the function with repeat sampling conducted 10,000 times in order to derive p-values that will provide improved coverage due to potential ties in the data comparisons. A small p-value indicated that the incubation period distributions are different, and the null hypothesis was rejected. We compared the resulting p-values to confirm if any variation observed was due to chance by calculating the proportion of p-values below 0. 05. The probability of obtaining at least the observed proportion of p-values less than 0.05 was calculated, and if it was less than 0.01, this provided statistical evidence for variation in incubation time distribution.

- **Identifying factors that explain heterogeneity**

In order to examine if the incubation period was influenced by the outbreak characteristics, we performed a linear mixed effect (random and fixed effects) analysis using the individual incubation period data provided as the dependent variable and the outbreak characteristics as the explanatory variables. We applied a square root transformation to the incubation period to reduce skewness of the data. Outbreak characteristics with sufficient information were included in a full multivariable model. Likelihood ratio tests was used as a means of attaining p-values by comparing the full model to an alternative model which excluded the variable of interest. A final model was developed by excluding variables without statistical significant association with incubation period ($p<0.1$).

So as to allow the inclusion of studies reporting only summary data (mean), we further performed a linear regression analysis. The effect of the explanatory variables on the mean incubation period was estimated by using a univariate model. Where statistical support for

an association was observed ($p<0.1$), a multivariate model was built which included the associated variables at that threshold to test for confounding.

Due to insufficient information, organism species was excluded as an explanatory variable in both analyses. The significance level for the final models was chosen to be 5%.

- **Identifying subgroups of studies for analysis**

In the presence of statistically significant heterogeneity, we explored the data using subgroup analyses. However, rather than randomly allocating studies to subgroups, we employed hierarchical cluster analysis to identify subgroups of studies that can be combined. The bootstrapped KS test was used to create a hierarchical cluster to show a graphical representation of how the studies grouped together in terms of their dissimilarities. We subtracted the p-values from one to generate a dissimilarity matrix showing the distances between the samples. The cluster analysis algorithm used was the complete linkage method. The output was a dendrogram showing compact visualisation of the dissimilarity matrix.

In order to reduce the likelihood of observing one significant result due to chance or making a type 1 error, we made pragmatic adjustments to the significance level (0.05) by dividing it by the number of studies included in the KS test which was 30. We then subtracted the adjusted p-value from 1 *(1- α)* to derive a cut-off point from which studies without evidence of heterogeneity can be defined within separate clusters. These clusters refer to subgroups of studies that do not have evidence of heterogeneity between them and can be combined for meta-analysis.

Subgroup analyses

We pooled the raw incubation data of studies within a subgroup to create a single dataset for each subgroup, and derived he following summary statistics:

- Number of studies included in a subgroup
- Total number of cases (sum of cases in all studies included in a subgroup)

- Mean and median incubation period of cases within a subgroup
- Standard deviation (SD), variance, skew and kurtosis of incubation period of cases within a subgroup

The mean attack rate of the studies within a subgroup was also calculated.

A forest plot showing the distribution of the mean incubation period and the corresponding 95% confidence interval was created. Studies without raw data (eight studies) were allocated to subgroups based on their reported mean and included in the forest plot, however, without a confidence interval as this could not be derived.

Risk of bias

We tested our data for 'small study-effect' using a funnel plot to visually examine the relationship between small sample sizes and incubation period.

Results

A total of 45,204 search results were retrieved from the three databases and the titles and abstracts were screened for relevance. Exclusion of articles considered irrelevant resulted in 682 articles, and after removing duplicates, 322 articles remained. An additional three articles were identified from searching through the reference list of review papers, resulting in 325 articles available for full text screening for incubation period data. Excluding articles that did not report incubation period and articles that did not meet the quality assessment criteria resulted in 60 articles remaining. These articles were further reviewed to ensure that the reported outbreaks were point source and the reported incubation period were accurate. Excluding outbreaks that were not point source (Appendix 2), 45 articles were included in the review (Figure 1). Four articles reported on two studies each bringing the number of studies included in the review up to 49 (Appendix 3). Of these, we were able to extract raw data from 30 studies.

Characteristics of studies included in the review

C. jejuni was the most commonly reported species accounting for 75.5% of included studies. Forty-five percent of the studies were published in year 2000 or later, and 81.6% were carried out in developed countries of Europe and North America (Table 3). Four studies were experimental and the remainder were epidemiological studies undertaken during outbreak investigations to identify the source of infection. Forty-six per cent of these (21/45) were retrospective cohort studies and 29% were descriptive studies.

The most common reported setting for outbreaks was private parties (14/49; 28.6%), including weddings and conference dinners, followed by farm visits (11/49; 22.4%). Poultry and dairy were the most frequently reported implicated food vehicle accounting for 40.8% (20/49) and 28.6% (14/49) respectively (Table 3). Comparing the food vehicle and setting of the outbreak, 50% of outbreaks caused by poultry dishes occurred at a private party, and 57.1% of outbreaks caused by dairy or dairy products occurred during a farm visit.

The funnel plot created to test for small study-effect resulted in a symmetric funnel indicating that the size of the study did not have any effect on the reported incubation period (results not shown). From the re-created epidemic curves, we observed a variation in the distribution of incubation period (Figure 2).

Test of heterogeneity

We calculated that the heterogeneity in the reporting of incubation periods across the different studies was I^2 = 72% (p-value for chi-squared = <0.00001). The proportion of p-values from the KS test that was below 0.05 was greater than 5% ((53%; 231/435). The probability of obtaining the resulting proportion was <0.00001.

These results indicate a variation in the distribution of incubation periods between studies which is not due to chance alone.

Factors that may explain heterogeneity

From the linear mixed-effects multivariable analysis and the likelihood ratio tests, age distribution and outbreak setting were significantly associated with incubation period, while food vehicle category showed a weak association with a p-value of 0.08 and met the inclusion criteria into the final model (Table 4). Age distribution and outbreak setting remained significantly associated with incubation period (p<0.01) in the final model after excluding the non-significant variables (attack rate and year of study) (Table 4).

From the linear regression univariate analysis, age distribution was the only variable with a significant association with the mean incubation period (p < 0.01) with outbreaks involving only children reporting a mean incubation period of 1.14 days longer when compared with mixed outbreaks involving both adults and children. In the final multi variable model also including outbreak setting, as one of the outbreak setting variables had met the inclusion criteria, the association with the mean incubation period remained significant(p<0.03) with outbreaks involving only children reporting a mean incubation period of 1.29 days longer when compared with mixed outbreaks involving both adults and children (Table 4).

Identifying subgroups of studies

Studies were paired and grouped based on evidence of dissimilarity. Studies found to have the least evidence of dissimilarity between them were paired. Likewise, some studies were not directly paired but attached to other pairs showing that the algorithm could not identify a single study with the least evidence of dissimilarity to them, but instead identified a pair of studies. The resulting output of this cluster analysis is presented as a dendrogram of the dissimilarity matrix (Figure 3).

Following the pragmatic adjustments made to the significance level, the resulting p-value was 0.0017 and the derived cut-off point was 0.9983. Five subgroups were identified using the cut point of 0.9983 to implement the p-value cut point of 0.0017, taking multiple testing into account. These comprised: a subgroup of eleven studies, a subgroup of eight studies and three subgroups of five, four and two studies. (Figure 3).

Summary of subgroup analyses

The subgroup containing eleven studies included 302 cases while the subgroup containing eight studies included 520 cases. The smallest subgroup with two studies also consisted of the lowest number of cases with 102 cases. The mean incubation period of studies in the subgroups varied between 2.5 days and 4.3 days (Table 5). There were also substantial differences in the variance, skew and kurtosis between subgroups (Table 5). There was some variation between the studies within subgroups (Figure 4) albeit not sufficient to evidence difference statistically.

The characteristics of four subgroups were quite similar in terms of the age distribution of cases and food vehicle (Table 6). These four subgroups included outbreaks which mostly reported poultry as the implicating food vehicle and at least 50% of the outbreaks involved only adults. Food services were reported as an outbreak setting in studies in four subgroups, however it was the predominant outbreak setting in subgroup 1. The characteristics of

subgroup 4 were different with 80% of outbreaks involving only children; dairy products and farm were the most commonly reported food vehicle and outbreak setting respectively.

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Discussion

Accurate estimations of the period between infection and onset of illness for any infectious disease are essential to support evidence based interventions in eliminating sources of infection. Our review identified that the reported estimations of the incubation period of campylobacteriosis varied widely, even within subgroups of studies. The results of the I^2 and KS tests show that this variation is not due to chance, and there is an underlying pattern of variation. Visual inspection of Figure 2 and the results in Table 5 show that heterogeneity is not only in relation to mean incubation period, but also the shape of the distribution. From both regression analyses, we identified age as a factor that may influence the distribution of incubation period, with reported incubation period in outbreaks affecting children longer than those in mixed age groups. The age structure of cases of campylobacter has changed in recent years with older people becoming increasingly affected [25], and this population shift was reflected in our review where outbreaks investigated after year 2000 mostly involved adults or mixed age groups, while prior to year 2000, more outbreaks involving children were reported.

Furthermore, there appears to be some association between the subgroup characteristics and implicated food vehicle, setting of outbreaks and age of affected cases. However, these differences do not explain all of the variation in distributions of incubation period between subgroups. This may be due to other factors influencing distribution of incubation period that are not evident in the studies or inaccuracy of measurement and reporting. Host characteristics such as underlying medical conditions and immune response [26] as well as dose response have been known to affect infectivity and susceptibility to *Salmonella*, and may also influence the incubation period of other bacterial infections. These individual patient details have not been provided in the reports, so it is not possible to examine the effect of these factors.

The results of our review might not be generalizable to low and middle income countries as majority of included outbreaks and experimental studies took place in high income countries in Europe and North America. Predisposing factors to campylobacteriosis in low and middle

income countries, which might also influence incubation period, have been reported to be malnutrition and antimicrobial resistance [27]. A further limitation of the current work is that case definitions varied between studies as authors used different criteria to define cases. The inclusion and exclusion of cases will therefore vary depending on the case definitions used, and this could also affect incubation period. However, all cases were identified at the onset of gastrointestinal symptoms including diarrhoea, vomiting and abdominal cramps, and all were in the context of a known outbreak or experimental study.

Outbreaks that mainly affected children were predominantly caused by consumption of raw milk or raw milk products and exposure was mostly during farm visits. This is similar to the report of Altekruse et al [28]. The incubation periods of outbreaks involving children were significantly longer than those of outbreaks involving adults or mixed age groups. A review of incubation period of infectious diseases in children reported a similar incubation period to our findings [29].

Our study identified poultry and unpasteurised milk as the most common implicating food vehicles and are known causes of transmission[30,31]. Studies have identified the presence of virulence genes in both poultry and dairy isolates [32]. However, there is a disparity in the prevalence of *Campylobacter* in different food products [32] which may result in a variation in acquiring infection as well as incubation period. Also, some type of foods have been known to affect infectivity and thus potentially incubation period of pathogens by being either protective or enabling; an example is fatty food acting as a buffer to protect *Salmonella* from gastric acid [26].

Infectious dose may have a substantial effect on incubation period distribution, although this may not have varied substantially in the experimental studies included in our review. Studies modelling the dose response of infectious diseases have reported a significant variation in the distribution of incubation period with dose [33,34]. Human experimental studies of *Campylobacter* [35] and *Salmonella* [36] showed shorter incubation period where the challenge dose was higher. One of the reviewed studies reported a dose response relationship between the amount of milk consumed and onset of illness and severity, where

cases drinking larger amounts of milk had shorter incubation periods and more severe symptoms [10]. A dose response relationship was also reported in a non-foodborne outbreak involving an outdoor bike race where shorter incubation periods were seen in cases who reported ingesting larger quantities of mud [13]. Another outbreak involving healthy military men who consumed at least four litres of untreated surface water during a military training exercise reported no dose response relationship between the quantity of water consumed and the severity of symptoms [37], however, there was no information on the relationship between ingested dose and incubation period. We were not able to analyse these relationships across the studies due to the lack of individual data related to dose and incubation time.

Host immunity could also influence the incubation period distribution as it determines if an exposure results in illness, and how long the process takes. The development of naturally acquired antibodies in response to a previous infection and the *C. jejuni* group antigen protects against subsequent illness [35], and may prolong incubation period if illness should occur.

It is worth noting that the bulk of the analyses has been carried out on a subset of studies included in the review from which raw data could be extracted. One problem we encountered in combining results of several studies was the different units of measurement used in reporting. Incubation periods were reported in hours, days or every two days. In order to combine the results, we converted all data to days, rounding up or rounding down where necessary. This could result in an over estimation where data was rounded up and an underestimation where data was rounded down and loss of precision for data from some studies. Furthermore, using the online data extraction tool, WebPlotDigitizer, required manual selection of data points which is open to human error. Separating experimental studies and outbreak reports into relevant subgroups would have been an ideal way of analysing the data, however there was insufficient information to carry out these analyses, as there were four experimental studies and only two of these reported the mean incubation period.

Exclusion of non-English language articles is appropriate if processing these is inefficient as in our research team and is unlikely to produce bias. Bias would require that non-English papers are associated with different incubation period distributions in outbreaks. However, if there are few eligible studies the translation and inclusion would be warranted. Furthermore, our study population is made up of cases that have been investigated as part of point source outbreaks where incubation period was not the main goal of investigation. This reduces the likelihood of publication bias and selection bias in our study population.

Our results confirm that incubation period in different outbreaks and experiments varied more than can be explained by chance, showed some clustering, and suggested that patient age may contribute to the variation. However, the information provided in the studies was not detailed enough to fully evaluate possible causes for these variations. The ideal data to support identification of factors affecting incubation period would be individual patient data across studies, including information such as underlying conditions, current medications and previous infections. In the absence of access to original individual patient data, reporting of outbreaks could allow better synthesis and meta-regression analysis. Although incubation period is not the main focus of outbreak reports they provide valuable natural experiments to describe incubation period distributions and identify factors affecting this. Increased awareness of the value of this aspect of outbreak reporting can improve the presentation of data to support their use in evidence synthesis.

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Conflict of interest:

The authors declare no conflict of interest.

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26. **Blaser MJ, Newman, LS**. A review of human salmonellosis: I. infective dose. *Review of Infectious Diseases* 1982; **4:** 1096–1106.

27. **Platts-Mills JA, Kosek M**. Update on the burden of *Campylobacter* in developing countries. *Current Opinion in Infectious Diseases* 2014; **27:** 444–450.

28. **Altekruse SF *et al.*** *Campylobacter jejun*i--an emerging foodborne pathogen. *Emerging Infectious Diseases* 1999; **5:** 28–35.

29. **European Centre for Disease Prevention and Control**. *Systematic Review on the incubation and infectiousness/shedding period of communicable diseases in children* European Centre for Disease Prevention and Control, Stockholm, 2016.

30. **Bianchini V *et al.*** Prevalence in bulk tank milk and epidemiology of *Campylobacter jejuni* in dairy herds in Northern Italy. *Applied and Environmental Microbiology* 2014; **80:** 1832–1837.

31. **El-Sharoud WM**. Prevalence and survival of *Campylobacter* in Egyptian dairy products. *Food Research International* 2009; **42:** 622–626.

32. **Modi S *et al.*** Prevalence of *Campylobacter* species in milk and milk products, their virulence gene profile and anti-bio gram. *Veterinary World* 2015; **8:** 1–8.

33. **Wood RM *et al.*** A dose and time response Markov model for the in-host dynamics of infection with intracellular bacteria following inhalation: with application to Francisella tularensis. *Journal of The Royal Society Interface* 2014; **11:** 20140119.

34. **Toth DJA *et al.*** Quantitative models of the dose-response and time course of inhalational anthrax in humans. *PLoS Pathogens* 2013; **9.**

35. **Black RE *et al.*** Experimental *Campylobacter jejuni* Infection in humans. *Journal of Infectious Diseases* 1988; **157:** 472–479.

36. **Waddington CS *et al.*** An outpatient, ambulant-design, controlled human infection model using escalating doses of Salmonella typhi challenge delivered in sodium bicarbonate solution. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 2014; **58:** 1230–1240.

37. **Aho M *et al.*** Waterborne outbreak of Campylobacter enteritis after outdoors infantry drill in Utti, Finland. *Epidemiology and Infection* 1989; **103:** 133.

570 *Table 1 Checklist for assessing incubation period data reported by individual studies*

571 *(adapted from Hawker et al)*

Criteria	Component
Exposure	• Clearly defined exposure e.g. identification of implicated food vehicle or source patient • Exposure linked epidemiologically or microbiologically to outcome • Exclusion of other potential sources
Diagnosis	• Microbiological confirmation (human, food or environmental confirmation) • Specific and sensitive case definition for clinical cases • Time constraints on case definitions to exclude very early or very late cases
Accuracy of measurement	• Clearly defined exposure time (point source or continuous exposure) • Reliability of onset times considering method and delay of data collection during epidemiological investigation • Accuracy of reported onset time (hourly, 6-hourly, daily)
Ascertainment of bias	• Identification of exposed group and reporting of onset on all or part of exposed group • Exclusion of background cases • Exclusion of secondary cases and person to person transmission when studying an environmental or foodborne source

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574 *Table 2 Details of data extracted from the studies*

Section	Information to be collected
General information	- Year of publication - Title of article - Authors - Type of publication (journals, conference abstract, grey literature, etc.) - PubMed ID (where applicable)
Study characteristics	- Year of study - Study design (cohort, case-control, experimental, case series) - Country of study - Age distribution - Comments on method or quality of study
Pathogen characteristics	- Infectious agent - Species - Subtype
Outcome data/ results	- Case definition - Reported incubation period (individual data, mean, median mode and range) - Derived or calculated summary estimates incubation period (raw data extracted) - Source of calculated data (epidemic curve or author

		description)
Other outcome data	-	Incubation period to particular symptoms
Factors that could affect incubation period	-	No of exposed cases
	-	No of people affected
	-	Setting
	-	Mode of transmission
	-	Food vehicle (for foodborne infections only)
	-	Patient characteristics (e.g. previous infection or treatment, underlying illness)
Any other relevant information	-	Any other relevant information

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576 *Table 3 Characteristics of studies included in review*

	N	%
Total number of studies	49	
Year of study		
Before year 2000	19	38.8
2000 and later	22	44.9
Unknown	8	16.3
Region of study		
Europe	20	40.8
North America	20	40.8
Australia	6	12.2
Asia	3	6.1
Species		
Campylobacter jejuni	37	75.5
Campylobacter coli	1	2.0
C. jejuni and *coli*	3	6.1
C. jejuni and *fetus*	1	2.0
Unknown	7	14.3
Age distribution		
Mixed ages	7	14.3
Children	15	30.6
Adult	27	55.1
outbreak setting		
Private party	14	28.6
Farm visit / animal contact	11	22.4
Restaurants	10	20.4
Outdoor activity	5	10.2

School	5	10.2
Experimental study	4	8.2
Food vehicle category		
Poultry	20	40.8
Dairy	14	28.6
Water	1	2.0
Other	7	14.3
Unknown	7	14.3

579 *Table 4 Linear mixed effect and regression models showing effect of study characteristics on mean incubation period.*

Characteristics	Linear mixed effect full model P-value of likelihood ratio test	Linear mixed effect final model P-value of likelihood ratio test	Linear regression univariate analysis Difference in mean incubation period	P-value	Linear regression multivariable analysis Difference in mean incubation period	P-value
Attack rate	0.10		-0.003	0.60		
Year of study	0.60					
After 2000			Reference			
Pre 2000			0.19	0.57		
Age distribution	<0.001	0.005				
Mixed ages			Reference		Reference	
Adults			0.30	0.45	0.08	0.84
Children			1.14	0.01	1.29	0.03
Outbreak setting	0.01	0.001				
Other			Reference		Reference	
Farm visit			0.31	0.47	-0.44	0.41

Private party			-0.09	0.80	0.05	0.89
Restaurant			-0.82	0.08	-0.65	0.15
School			-0.43	0.37	-0.63	0.34
Food vehicle category	0.08	0.06				
Other			Reference			
Dairy			-0.03	0.95		
Poultry			-0.41	0.45		

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Table 5 Summary statistics of subgroups

	Frequency	Sum of cases	Attack rate	Median	Mean (95% CI)	Variance	Skew	Kurtosis
Subgroup 1	11	302	45.1	2	2.5 (2.3 – 2.7)	2.1	1.5	4.6
Subgroup 2	8	520	44.4	3	3.2 (3.1 – 3.4)	2.5	1.3	2.2
Subgroup 3	2	102	26.4	3	3.3 (3.1 – 3.5)	1.0	0.3	-0.9
Subgroup 4	5	208	51.3	4	4.1 (3.9 – 4.3)	2.7	1.4	3.3
Subgroup 5	4	145	46.4	4	4.3 (3.9 – 4.7)	4.7	0.8	2.0

584 *Table 6 Characteristics of studies within subgroups*

Characteristics	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Subgroup 5
Age	63% adults	63% adults	50% adults	80% children	50% adults
Food vehicle	63.6% Poultry	50% poultry 25% dairy	100% poultry	60% dairy 20% poultry	50% poultry
Setting of outbreaks	55% Food service	25% farm 25% school 25% food service	50% food service 50% school	40% farm 20% school	50% food service 50% school
Severity of illness	63%	50%	50%	80%	100%
Duration of illness	0 – 24 days	0 – 20 days	1-6 days	0-18 days	1-9 days
Longest incubation period	10 days	8 days	5 days	11 days	14 days

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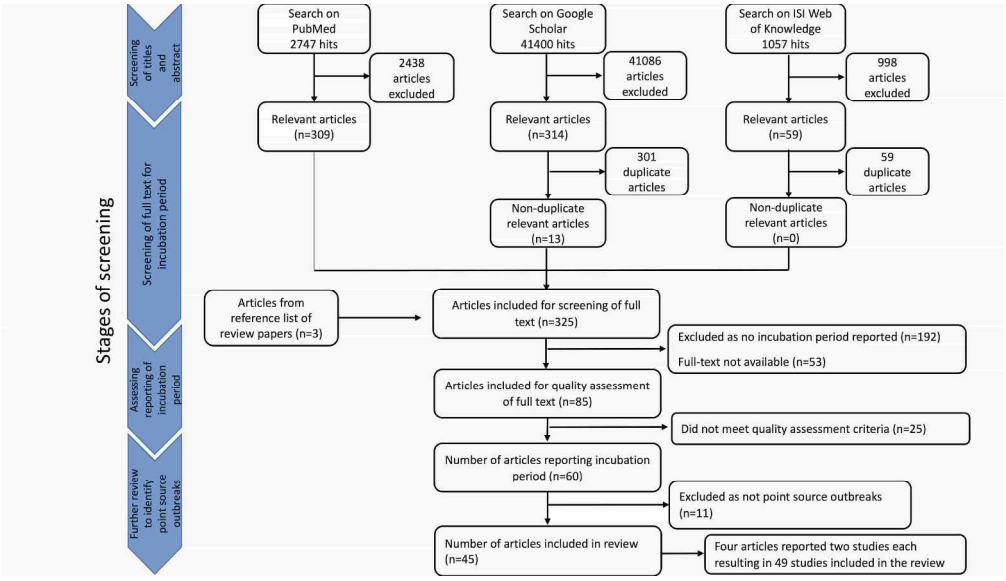
Legend for figures

Figure 1 Flowchart of study selection process

Figure 2 Collated epidemic curves re-created from raw data and arranged according to subgroups

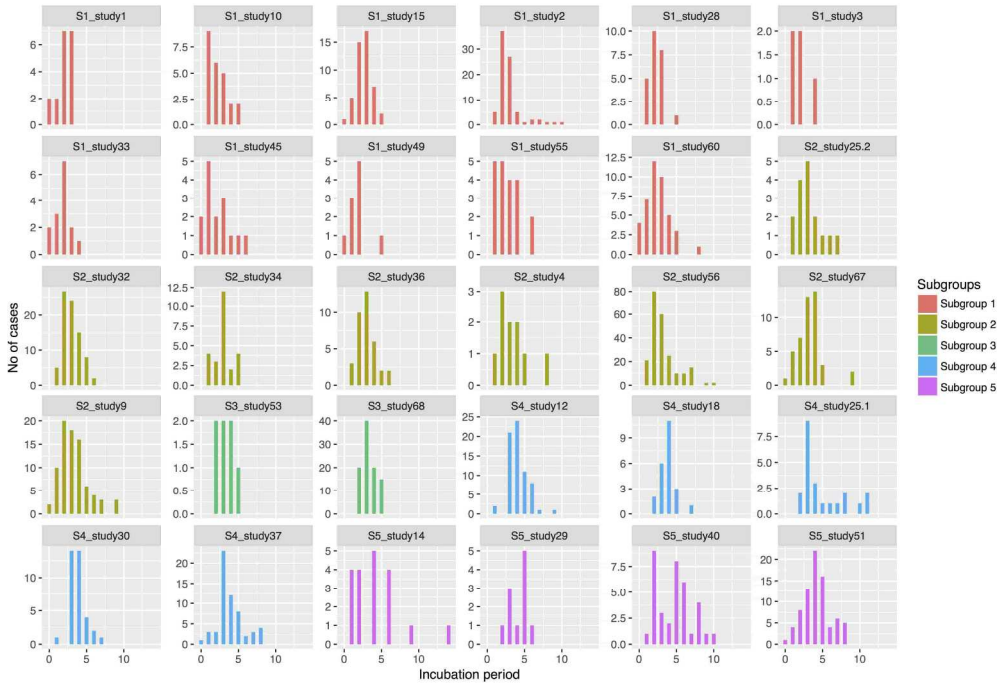
Figure 3 Dendrogram showing compact visualization of dissimilarity matrix and identified subgroups.

Figure 4 Forest plot showing mean incubation period and 95% CI



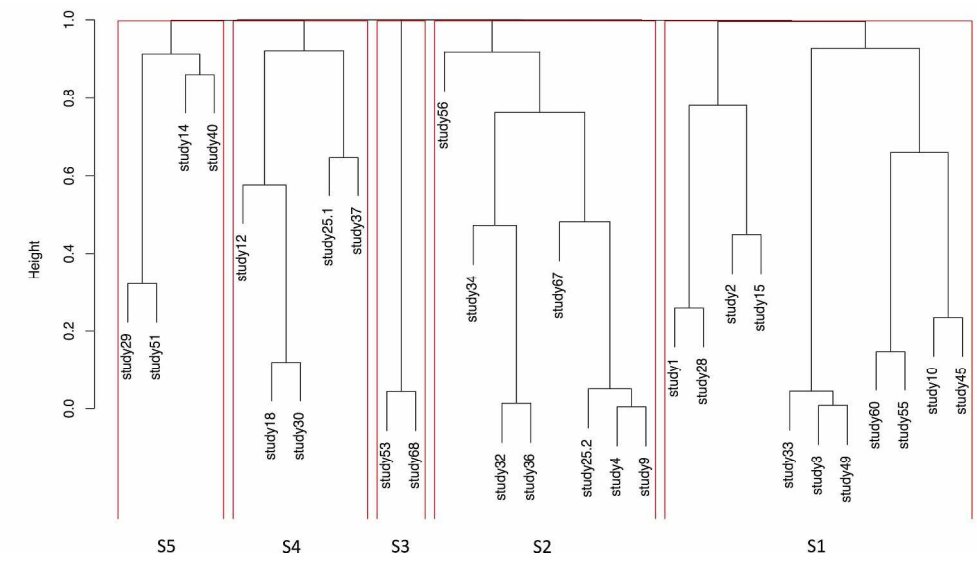
Flowchart of study selection process

1760x1003mm (72 x 72 DPI)



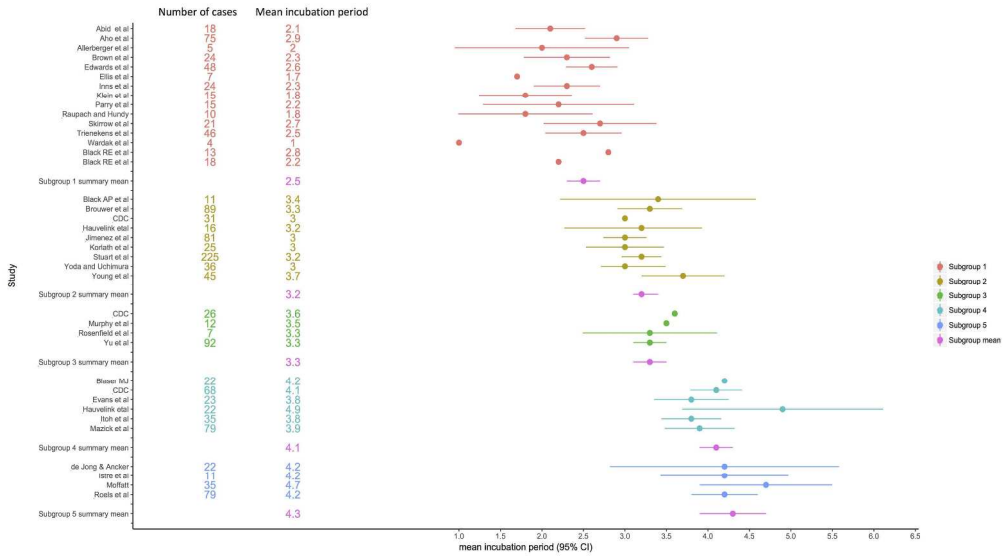
Collated epidemic curves re-created from raw data and arranged according to subgroups

1563x1068mm (72 x 72 DPI)



Dendrogram showing compact visualization of dissimilarity matrix and identified subgroups

1729x948mm (72 x 72 DPI)



Forest plot showing mean incubation period and 95% CI

1777x1002mm (72 x 72 DPI)

Appendix 1. MeSH terms used in search strategy

Search strategy:

Terms for

I. Campylobacter

II. Humans

III. Outbreaks

IV. Experimental

I. ("campylobacter"[MeSH Terms] OR "campylobacter"[All Fields])

AND II (I AND II)

II. ("humans"[MeSH Terms] OR "humans"[All Fields])

AND III (I AND II AND III)

III. ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "outbreaks"[All Fields] OR "disease outbreaks"[MeSH Terms] OR ("disease"[All Fields] AND "outbreaks"[All Fields]) OR "disease outbreaks"[All Fields])

I AND II AND (I AND II AND IV)

IV. experimental [All Fields]

Appendix 2 List of studies excluded from review and reason for exclusion

Title	Reason for exclusion
Blaser et al. *Campylobacter* enteritis associated with foodborne transmission. *American Journal of Epidemiology* 1982; 116:886 – 894.	Non-point source outbreak. Two possible outbreaks overlapping.
Blaser et al. Outbreaks of *Campylobacter* enteritis in two extended families: evidence for person-to-person transmission. *The Journal of Paediatrics* 1981; 98:254-257.	Non-point source outbreak, secondary transmission evident
Braeye et al. A large community outbreak of gastroenteritis associated with consumption of drinking water contaminated by river water, Belgium, 2010. *Epidemiology and Infection* 2015; 143:711-719.	Difficult to distinguish between primary and secondary cases
Centre for Disease Prevention and Control. Multistate outbreak of *Campylobacter jejuni* infections associated with undercooked chicken livers — Northeastern United States, 2012. *Morbidity and mortality weekly report* 2013; 62:874-875.	Incubation period not reported
Centre for Disease Prevention and Control. Outbreak of *Campylobacter jejuni* infections associated with drinking unpasteurized milk procured through a cow-leasing program --- Wisconsin, 2001. *Morbidity and mortality weekly report* 2002; 51:548-549.	Exposure time not clearly defined
de Perio MA et al. *Campylobacter* infection in poultry-processing workers, Virginia, USA, 2008–2011. *Emerging Infectious Diseases* 2013; 19:286-288.	Prolonged exposure

DeFraites RF et al. An outbreak of *Campylobacter* enteritis associated with a community water supply on a U.S. military installation. *Medical Surveillance Medical Report* 2014; 21:10-15.	Continuous exposure
Deming MS et al. *Campylobacter* enteritis at a university: transmission from eating chicken and from cats. *American Journal of Epidemiology* 1987; 126:526-534.	Exposure time not clearly defined
Engberg J et al. Water-borne *Campylobacter jejuni* infection in a Danish town-a 6-week continuous source outbreak. **Clinical Microbiology and Infection** 1998; 4:648-656.	Continuous exposure
Fahey et al. An outbreak of *Campylobacter jejuni* enteritis associated with failed milk pasteurisation. *Journal of Infection* 1995; 31:137-143.	Exposure time not clearly defined
Finch MJ and Blake PA. Foodborne outbreaks of Campylobacteriosis: The United States experience. *American Journal of Epidemiology* 1985; 122:262-268.	Review of several outbreaks some of which are already included in the review
Gardner TJ et al. Outbreak of campylobacteriosis associated with consumption of raw peas. *Clinical Infectious Diseases* 2011; 53:26-32.	Extended exposure period
Graham C et al. Outbreak of campylobacteriosis following pre-cooked sausage consumption. *Australian and New Zealand Journal of Public Health* 2005; 29:507-510.	Non-point source outbreak. Exposure happened over 2 days
Gubbels S et al. A waterborne outbreak with a single clone of *Campylobacter jejuni* in the Danish town of Køge in May 2010. *Scandinavian Journal of Infectious Diseases*	Continuous exposure

2012; 44:586-594.	
Gunnarsson H and Swedhem Å. The usefulness of Diffusion-In-Gel-ELISA in clinical practice as illustrated by a *Campylobacter jejuni* outbreak. *Journal of Immunological Methods* 1998; 215:135-144.	Not much information to confirm if outbreak is point source
Hennessy EP. An outbreak of campylobacteriosis amongst directing staff and students at the infantry training centre, Brecon, Wales, March 2004. *Journal of the Royal Army Medical Corps* 2004; 150:175-178.	Exposure time not clearly defined
Horn BJ and Lake RJ. Incubation period for campylobacteriosis and its importance in the estimation of incidence related to travel. *Euro Surveillance: European Communicable Disease Bulletin* 2013; 18.	Incubation period reported for proportion of cases not individual cases
Jakopenac I et al. A large waterborne outbreak of campylobacteriosis in Norway: the need to focus on distribution system safety. *BMC Infectious Diseases* 2008; 8:128.	Exposure time not clearly defined
Kuusi M et al. A large outbreak of campylobacteriosis associated with a municipal water supply in Finland. *Epidemiology and Infection* 2005; 133:593-601.	Exposure time not clearly defined
McNaughton RD et al. Outbreak of *Campylobacter* enteritis due to consumption of raw milk. *Canadian Medical Association Journal* 1982; 126:657.	Exposure time not clearly defined
Mentzing L. Waterborne outbreaks of *Campylobacter* enteritis in Central Sweden. *The*	Exposure time not clearly defined

Lancet 1981; 318:352-354.	
Møller-Stray J et al. Two outbreaks of diarrhoea in nurseries in Norway after farm visits, April to May 2009. *Euro Surveillance: European Communicable Disease Bulletin* 2012; 17.	Incubation period not reported
Morgan D et al. An outbreak of *Campylobacter* infection associated with the consumption of unpasteurised milk at a large festival in England. *European Journal of Epidemiology* 1994; 10:581-585.	Exposure time not clearly defined. Exposure possibly occurred over 3 days at a festival
O'Leary MC et al. A continuous common-source outbreak of campylobacteriosis associated with changes to the preparation of chicken liver pâté. *Epidemiology and Infection* 2009; 137:383-388.	Exposure time not clearly defined. Exposure occurred at intervals when cases dined
Porter IA and Reid TM. A milk-borne outbreak of *Campylobacter* infection. *The Journal of Hygiene* 1980; 84:415.	Exposure time not clearly defined. Date of exposure unknown, as raw milk was distributed on a certain day but day of actual consumption not recorded.
Potter ME et al. Human *Campylobacter* infection associated with certified raw milk. *American Journal of Epidemiology* 1983; 11:475-483.	Incubation period not reported
Riordan T et al. A point source outbreak of *Campylobacter* infection related to bird-	Exposure time not clearly defined

pecked milk. *Epidemiology and Infection*; 110:261.	
Rogol M et al. Waterborne outbreak of *Campylobacter* enteritis. *European Journal of Clinical Microbiology* 1983; 2:588-590.	Exposure time not clearly defined
Sacks JJ et al. Epidemic campylobacteriosis associated with a community water supply. *American Journal of Public Health* 1986; 76:424-428.	Exposure time not clearly defined
Taylor DN et al. Waterborne transmission of *Campylobacter* enteritis. *Microbial Ecology* 1982; 8:347-354.	Incubation period not reported
Tettmar RE and Thornton EJ. An outbreak of *Campylobacter* enteritis affecting an operational Royal Air Force unit. *Public Health* 1981; 95:69-73.	Exposure time not clearly defined
Unicomb LE et al. Outbreaks of Campylobacteriosis in Australia, 2001 to 2006. *Foodborne Pathogens and Disease* 2009; 6:1241-1250.	Not point source outbreak
Vierikiko A et al. Domestically acquired *Campylobacter* infections in Finland. *Emerging Infectious Diseases* 2004; 10:127-130.	Incubation period not reported
Wood RC et al. *Campylobacter* enteritis outbreaks associated with drinking raw milk during youth activities: A 10-year review of outbreaks in the United States. *Journal of the American Medical Association* 1992; 268:3228-3230.	Not point source outbreak
Yanagisawa S. Large outbreak of *Campylobacter* enteritis among school children. *The*	Incubation period not reported

Lancet 1980; 316:153.	
Zeiger M et al. Outbreak of campylobacteriosis associated with a long-distance obstacle adventure race--Nevada, October 2012. *Morbidity and mortality weekly report* 2014; 63:375-378.	Exposure time not clearly defined. Exposure was an outdoor event that took place over two days.

Appendix 3 List of studies included in the review

Study number	Title
study1	**Abid M. et al.** Duck liver–associated outbreak of campylobacteriosis among humans, United Kingdom, 2011. *Emerging Infectious Diseases* 2013; 8: 1310 - 1313.
study2	**Aho M. et al.** Waterborne outbreak of *Campylobacter* enteritis after outdoors infantry drill in Utti, Finland. *Epidemiology and Infection* 1989; 103: 133.
study3	**Allerberger F. et al.** Barbecued chicken causing a multi-state outbreak of *Campylobacter jejuni* enteritis. *Infection* 2003; 31: 19-23.
study4	**Black A. et al.** *Campylobacter* outbreak due to chicken consumption at an Australian capital territory restaurant. *Communicable Diseases Intelligence Quarterly Report* 2006; 30: 373-377
study5a	**Black R. et al.** Experimental *Campylobacter jejuni* Infection in humans. *Journal of Infectious Diseases* 1988; 157: 472-479
study5b	**Black R. et al.** Experimental *Campylobacter jejuni* Infection in humans. *Journal of Infectious Diseases* 1988; 157: 472-479
study7	**Blaser M. et al.** The influence of immunity on raw milk— associated *Campylobacter* infection. *JAMA* 1987; 257: 43-46
study9	**Brouwer R. et al.** An explosive outbreak of *Campylobacter* enteritis in soldiers. *Antonie van Leeuwenhoek* 1979; 45: 517-519
study10	**Brown P. et al.** An outbreak of food-borne *Campylobacter jejuni* infection and the possible role of cross-contamination. *Journal of Infection* 1988; 17: 171-176.
study11	**Centers for Disease Control and Prevention (CDC).** Outbreak of *Campylobacter* enteritis associated with cross-contamination of food--Oklahoma, 1996. *Morbidity and mortality weekly report* 1998; 47: 129-131.
study12	**Centers for Disease Control and Prevention (CDC).** *Campylobacter jejuni* infection associated with unpasteurized milk and cheese--Kansas, 2007.

Morbidity and mortality weekly report 2009; 57: 1377-1379

study14 **de Jong B. and Ancker C.** Web-based questionnaires - a tool used in a *Campylobacter* outbreak investigation in Stockholm, Sweden, October 2007. *Euro Surveillance: European Communicable Disease Bulleti*n 2008; 13.

study15 **Edwards D. et al.** Campylobacteriosis outbreak associated with consumption of undercooked chicken liver pâté in the East of England, September 2011: identification of a dose-response risk. *Epidemiology and Infection* 2014; 142: 352-357.

study16 **Ellis A. et al.** Outbreak of *Campylobacter* infection among farm workers: an occupational hazard. *Canada Communicable Disease Report* 1995; 21: 153-156.

study17 **Evans M. et al.** A *Campylobacter* outbreak associated with stir-fried food. *Epidemiology and Infection* 1998; 121: 275 - 279.

study18 **Evans M. et al.** A milk-borne *Campylobacter* outbreak following an educational farm visit. *Epidemiology and Infection* 1996; 117: 457

study20 **Farmer S. et al.** Food-borne *Campylobacter* outbreak in Liverpool associated with cross-contamination from chicken liver parfait: Implications for investigation of similar outbreaks. *Public Health* 2012; 126: 657 - 659.

study22 **Goodman L. et al.** A restaurant associated *Campylobacter* outbreak. *European Journal of Clinical Microbiology* 1983; 2: 394-395.

study25a **Hauvelink A. et al.** Two outbreaks of campylobacteriosis associated with the consumption of raw cows' milk. *International Journal of Food Microbiology* 2009; 134: 70-74.

study25b **Hauvelink A. et al.** Two outbreaks of campylobacteriosis associated with the consumption of raw cows' milk. *International Journal of Food Microbiology* 2009; 134: 70-74.

study26 **Hope K. et al.** Short incubation periods in *Campylobacter* outbreaks associated

with poultry liver dishes. *Communicable Diseases Intelligence Quarterly Report* 2014; 38: 20-23.

study28 **Inns T. et al.** Cohort study of a campylobacteriosis outbreak associated with chicken liver parfait, United Kingdom, June 2010. *Euro Surveillance: European Communicable Disease Bulletin* 2010; 15.

study29 **Istre G. et al.** *Campylobacter* enteritis associated with undercooked barbecued chicken. *American Journal of Public Health* 1984; 74: 1265-1267.

study30 **Itoh T. et al.** An outbreak of acute enteritis due to *Campylobacter fetus* subspecies *jejuni* at a nursery school in Tokyo. *Microbiology and Immunology* 1980; 24: 371-379.

study32 **Jimenez M. et al.** An outbreak of *Campylobacter jejuni* enteritis in a school of Madrid, Spain. *Euro Surveillance: European Communicable Disease Bulletin* 2005; 10:118-121

study33 **Klein B. et al.** *Campylobacter* infection associated with raw milk: An outbreak of gastroenteritis due to *campylobacter jejuni* and thermotolerant *campylobacter fetus* subsp *fetus. JAMA* 1986; 255: 361-364

study34 **Korlath J. et al.** A point-source outbreak of campylobacteriosis associated with consumption of raw milk. *Journal of Infectious Diseases* 1985; 152: 592-596.

study36 **Yoda K. and Uchimura M.** An outbreak of *Campylobacter jejuni* food poisoning caused by secondary contamination in cooking practice at a high school. *Japanese Journal of Infectious Diseases* 2006; 59: 408-409.

study37 **Mazick A. et al.** An outbreak of *Campylobacter jejuni* associated with consumption of chicken, Copenhagen, 2005. *Euro Surveillance: European Communicable Disease Bulletin* 2006; 11.

study40 **Moffatt C. et al.** *Campylobacter jejuni* gastroenteritis at an Australian boarding school: consistency between epidemiology, flaA typing, and multilocus sequence typing. *Foodborne Pathogens and Disease* 2010; 7: 1285-1290.

study43	**Murphy O. et al.** An outbreak of C*ampylobacter* food poisoning in a health care setting. *Journal of Hospital Infection* 1995; 30: 225-228.
study45	**Parry A. et al.** 'Surprise': Outbreak of *Campylobacter* infection associated with chicken liver pâté at a surprise birthday party, Adelaide, Australia, 2012. *Western Pacific Surveillance and Response Journal: WPSAR* 2012; 3: 16-19
study46	**Peterson M.** *Campylobacter jejuni* enteritis associated with consumption of raw milk. *Journal of Environmental Health* 2003; 65: 20-21.
study49	**Raupach J. and Hundy R.** An outbreak of *Campylobacter jejuni* infection among conference delegates. *Communicable Diseases Intelligence Quarterly Report* 2003; 27: 380-383.
study51	**Roels T. et al.** A foodborne outbreak of *Campylobacter jejuni* (O:33) infection associated with tuna salad: a rare strain in an unusual vehicle. *Epidemiology and Infection* 1998; 121: 281-287
study53	**Rosenfield J. et al.** Serotyping of *Campylobacter jejuni* from an outbreak of enteritis implicating chicken. *Journal of Infection* 1985; 11: 159-165.
study55	**Skirrow M. et al.** An outbreak of presumptive food-borne *Campylobacter* enteritis. *Journal of Infection* 1981; 3:234-236.
study56	**Stuart T. et al.** Campylobacteriosis outbreak associated with ingestion of mud during a mountain bike race. *Epidemiology and Infection* 2010; 138: 1695-1703
study59a	**Tribble D. et al.** Assessment of the duration of protection in *Campylobacter jejuni* experimental infection in humans. *Infection and Immunity* 2010; 78: 1750-1759.
study59a	**Tribble D. et al.** Assessment of the duration of protection in *Campylobacter jejuni* experimental infection in humans. *Infection and Immunity* 2010; 78: 1750-1759.
study60	**Trienekens S. et al.** Don't count your chicken livers: an outbreak of *Campylobacter sp.* not associated with chicken liver parfait, England, November

2013. *PLoS currents* 2014; 6.

study63 **Wardak S. et al.** The first report on *Campylobacter coli* family outbreak detected in Poland in 2006. *Euro Surveillance: European Communicable Disease Bulletin* 2008; 13.

study64 **Winquist A. et al.** Outbreak of Campylobacteriosis at a senior center. *Journal of the American Geriatrics Society* 2001; 49: 304-307.

study67 **Young N. et al.** *Campylobacter* infection associated with consumption of duck liver pâté: a retrospective cohort study in the setting of near universal exposure. *Epidemiology & Infection* 2014; 142: 1269-1276.

study68 **Yu J. et al.** Epidemiology of *Campylobacter jejuni* outbreak in a middle school in Incheon, Korea. *Journal of Korean Medical Science* 2010; 25: 1595-1600.

study70a **Centers for Disease Control and Prevention (CDC).** Campylobacteriosis associated with raw milk consumption -- Pennsylvania

study70b **Centers for Disease Control and Prevention (CDC).** Campylobacteriosis associated with raw milk consumption -- Pennsylvania

study71 **Centers for Disease Control and Prevention (CDC).** Epidemiologic notes and reports *Campylobacter* outbreak associated with certified raw milk products -- California

study72 **Centers for Disease Control and Prevention (CDC).** Epidemiologic notes and reports *Campylobacter* outbreak associated with raw milk provided on a dairy tour -- California