

# A meta-analysis of case-control studies examining sporadic campylobacteriosis in Australia and New Zealand from 1990 to 2016

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Australia and New Zealand experience some of the highest rates of human campylobacteriosis in the industrialised world.<sup>1</sup> *Campylobacter* is the most commonly notified cause of bacterial gastroenteritis in Australia,<sup>2</sup> with a notification rate of 146.9/100,000 population in 2016.<sup>3</sup> In New Zealand, campylobacteriosis continues to be the most commonly notified disease with a notification rate of 158.9/100,000 population in 2016.<sup>4</sup> These rates are high compared to other high-income countries, even with the decline in incidence due to interventions in the poultry meat industry in the past decade.<sup>5</sup> Current surveillance systems also underestimate the true burden of disease, with an estimated additional 10 cases in the community for every notified case in Australia,<sup>6</sup> and an additional 10–30 cases for every notified case in New Zealand.<sup>7</sup> Approximately 77% of human *Campylobacter* infections in Australia are thought to be foodborne in origin.<sup>2,8</sup> Infections are also spread via waterborne and zoonotic routes, with occasional reports of person-to-person transmission.<sup>9</sup> Globally, the major risk factors for foodborne transmission are consumption of contaminated or undercooked meats (especially poultry meat), consumption of offal, and consumption of raw milk.<sup>1,10</sup> *Campylobacter* infections are commonly sporadic in nature rather than outbreak-related.<sup>11</sup> In Australia during the period 2001 to 2006, 33 outbreaks were identified,

## Abstract

**Objective:** We conducted a meta-analysis of case-control studies to identify locally relevant risk factors for sporadic campylobacteriosis in Australia and New Zealand.

**Methods:** We searched Medline, Web of Science, ProQuest and Google Scholar using PRISMA guidelines. Reference lists and grey literature were hand-searched. Meta-analyses were conducted in the R package 'metafor' using published odds ratios and 95% confidence intervals.

**Results:** We identified 325 articles, from which we included 10 that described case-control studies. Four risk factors were statistically significant in the meta-analysis: eating undercooked poultry (OR=4.28, 95%CI 3.09-5.93); eating poultry cooked outside the home (OR=2.13, 95%CI 1.66-2.72); having pet chickens (OR=3.29, 95%CI 2.12-5.10); and overseas travel (OR=5.55, 95%CI 3.20-9.63). Among children, having pet dogs showed elevated but not significant risk (OR=1.57, 95%CI 0.99-2.49).

**Conclusions:** We identified consumption of chicken meat and contact with domestic chickens as important risk factors for campylobacteriosis in Australia and New Zealand.

**Implications for public health:** While consumption of chicken meat is a well-known risk factor for campylobacteriosis, zoonotic transmission is often overlooked. This research indicates a greater need for public health awareness surrounding zoonotic campylobacteriosis, especially for young children.

**Key words:** campylobacteriosis, Australia, New Zealand, meta-analysis

affecting 457 people.<sup>12</sup> This included 147 laboratory-confirmed cases, which accounted for just 0.1% of campylobacteriosis notifications for the time period.<sup>12</sup> Considering the low proportion of human campylobacteriosis cases that are outbreak-related and given that previous studies in the northern hemisphere have shown that the predominant sources of sporadic infection may differ from those of outbreaks,<sup>10</sup> relying on outbreak data may result in incorrect

conclusions about causes of sporadic infection. A separate review of locally published studies assessing risk factors for sporadic infections as opposed to those in an outbreak setting is warranted.

This meta-analysis focuses on papers using the case-control study design to investigate locally relevant risk factors for sporadic campylobacteriosis in Australia and New Zealand.

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## Methods

### Literature search

We searched Medline, Web of Science, ProQuest, and Google Scholar for papers published between 1990 and April 2017 and included studies relevant to humans. Reference lists and grey literature sources were also hand-searched. Grey literature sources included unpublished studies, theses and dissertations. The number of studies identified at each step were recorded, as per PRISMA reporting guidelines.<sup>13</sup>

For Medline, our search criteria included MeSH subject headings "Campylobacter infections"; "Campylobacter" (exploded) and "Risk Factors"; and either "Australia" (exploded) or "New Zealand". Additionally, the keywords "source\*" and "cause\*" were included in the search. For both Web of Science and ProQuest, keywords included "Campylobacter\*"; "human\*"; "Australia\*" or "New Zealand", and "risk factor\*"; "source\*" or "cause\*". For ProQuest, we restricted the search to papers including these terms in the abstract. ProQuest databases searched included all those in the 'health and medicine' and 'science and technology' categories.

Citations were collected and managed in EndNote (version X8). All relevant studies were published in English.

We referred to MOOSE guidelines to ensure all appropriate reporting criteria were considered in this meta-analysis.<sup>14</sup>

### Relevance screening

References were collated, summarised and reviewed for inclusion using the following criteria: 1) the study includes data on human *Campylobacter* infection; 2) the data were collected in Australia or New Zealand; 3) the study was published during or after 1990; 4) the study investigates risk factors for sporadic disease; and 5) the article describes a case-control study. Papers were excluded if they used data that were in another more robust publication. Initial screening was conducted by one reviewer and identified papers were considered by four additional reviewers. Papers excluded at each step were noted, as per PRISMA guidelines (flow diagram template found at [www.prisma-statement.org](http://www.prisma-statement.org)).

### Quality assessment

Newcastle-Ottawa Scale ratings were used to assess the quality of studies to be included

and study quality.<sup>15</sup> Age was selected as the most important factor to be controlled for. Papers controlling for any additional potential confounder received a second star.

### Meta-analysis

For the meta-analyses, only studies where odds ratios (ORs) and their 95% confidence intervals (CIs) were reported were included. Meta-analyses include calculations of  $I^2$  values to assess heterogeneity. A cut-off  $I^2$  value of 50% (considered 'moderate' heterogeneity)<sup>16</sup> was used to select variables for meta-analysis, although those with higher  $I^2$  values were considered in sensitivity analysis. The R package 'metafor'<sup>17</sup> was used for all meta-analyses. Where published, adjusted ORs (aORs) were used. Results were weighted based on individual study sizes.

Risk factors were compared between studies and those with ORs and 95% CIs reported in three or more studies underwent meta-analysis. A mixed-effects model (random-effects plus moderators) was selected for meta-analysis to account for heterogeneity between studies and weighting based on study size.<sup>18,19</sup> This was necessary as each study was designed and conducted differently, on various select populations and for different time periods over the course of 27 years.<sup>20</sup>

## Results

We identified 325 titles, with 261 excluded after relevance screening. The remaining 64 full-text records were assessed for eligibility, with 23 not reporting ORs; 29 were outbreak investigations and two included datasets that overlapped with other records. Data were extracted from the remaining 10 studies for inclusion in meta-analyses (Figure 1). The number of cases in these case-control studies ranged from 26 to 881 (Table 1).<sup>11,21-29</sup>

### Demographic characteristics

Of the 10 case-control studies, three studies focussed on risk factors in young children, with this age category described as <3 years,<sup>28</sup> 0–4 years<sup>27</sup> and 1–5 years.<sup>23</sup> Three other studies excluded young children, defining the population as aged  $\geq 5$  years,<sup>11</sup>  $\geq 15$  years<sup>26</sup> and  $\geq 20$  years.<sup>21</sup> One study collected epidemiological information for all ages, and then separated participants into those aged 0–4 years and  $\geq 5$  years when considering age-specific risk factors.<sup>29</sup> Of

the six papers that described the gender of participating cases, four identified a higher percentage of male cases (range 53.2–60.0%).<sup>11,23,25,28</sup>

Half of the papers did not describe the urban/rural distribution of cases.<sup>11,21-23,27</sup> Of the remaining five studies, one reported 85.7% of cases living in an urban setting,<sup>24</sup> one study was based entirely in a regional setting<sup>29</sup> and two focused exclusively on urban cases.<sup>25,26</sup> The remaining study described the area that cases were recruited from as being "predominantly urban".<sup>28</sup>

### Study quality

Newcastle-Ottawa Scale ratings for these studies ranged from two to eight, with a median score of seven (maximum possible score is nine). The Neal and Bloomfield study<sup>26</sup> was the only major outlier with a score of two. With one of the smallest sample sizes, this study has little impact on the overall results of the meta-analyses.

### Risk factors

Half (5/10) of the case-control studies identified consumption of chicken or poultry meat as a statistically significant risk factor for infection.<sup>11,24-26,29</sup> One study identified the consumption of roast beef eaten at a restaurant as being associated with infection.<sup>29</sup> Consumption of offal<sup>11</sup> and consumption of raw dairy<sup>24</sup> products were each statistically significant risk factors in only one study.

Five of the 10 studies identified puppies or pet dogs as a risk factor, with three identifying pet chickens as a risk factor. Zoonotic risk factors were especially common in young children (zoonotic risk factors were identified nine times in total, four of which were in studies only investigating risk factors in young children), whereas consumption of chicken or poultry meat was not identified as a risk factor in this age group.

In a study targeting infants, Tenkate and Stafford<sup>28</sup> identified a strong association between consumption of mayonnaise and campylobacteriosis (aOR=4.13, 95%CI 1.61-10.59,  $p=0.003$ ). However, less than one-quarter of cases indicated that they had eaten mayonnaise (17/76 (22.4%), and 11/142 (7.7%) of controls. While it is biologically plausible that mayonnaise could be a vehicle for *Campylobacter*,<sup>30</sup> the authors indicated that this association was most likely a random or systematic error.

Stephens<sup>27</sup> identified sausages as a significant risk factor for campylobacteriosis in young children ( $\leq 5$  years old) when adjusting for age, state and household income (aOR=2.0, 95%CI 1.2-3.2). The population attributable risk proportion estimate was 30.5%, with 54% of cases and 44% of controls indicating they had consumed sausages in the relevant time period. Sausages were not identified as a risk factor in persons aged over five years in the concurrent study of this population;<sup>11</sup> however, frequency of consumption was considerably less (28% in cases and 26% in controls).<sup>27</sup> Unfortunately, the risk factor 'sausages' was non-specific and it is unclear which meat(s) were consumed. Sausages have previously been implicated as a source of both sporadic and outbreak-related *Campylobacter* infection<sup>31,32</sup> and the authors of this study outlined the biological plausibility of sausages as a vehicle for infection. However, they expressed uncertainty when describing this variable, unsure if it is a causal association or the result of random or systematic error.

Exposure to diarrhoeal illness or contact with a sick person was identified as a risk factor in two studies, with swimming and consumption of rainwater each identified as risk factors in one study. One study excluded participants who had travelled overseas during the exposure period,<sup>21</sup> while two other studies excluded these from analyses investigating locally relevant risk factors only.<sup>11,29</sup> Overseas travel was determined to be a significant risk factor for sporadic campylobacteriosis in four of the studies that included these participants (4/10).

### Meta-analysis

The following risk factors were identified for meta-analysis: eating undercooked poultry; eating poultry not cooked at home; overseas travel; having pet chickens; and having pet dogs. These risk factors were initially investigated across all age groups.

The variable 'having pet dogs' showed high levels of heterogeneity in meta-analysis:  $I^2=69.6\%$ . The same issue was present when looking only at pet dogs aged less than six months ( $I^2=89.5\%$ ). When limited to studies looking at young children with pet dogs, heterogeneity was less; however, 'having pet dogs' did not reach significance in meta-analysis, with an overall OR=1.57 (95%CI 0.99-2.49). It should be noted that in each of these meta-analyses most studies had small sample sizes and large confidence intervals, with one

study in each meta-analysis providing the majority of weight, which may skew results. The forest plots for 'having pet dogs' as a risk factor for human campylobacteriosis are shown in Supplementary File 1.

Each of the remaining meta-analyses were evaluated to have low levels of heterogeneity ( $I^2$  less than 25%).<sup>16</sup> However, some required grouping of risk factors that weren't identical. Variability in risk factors are described below.

The meta-analysis for 'eating undercooked poultry' grouped risk factors that were similar, namely: eating undercooked poultry and eating undercooked chicken. Two studies only reported crude ORs, with the other studies reporting aORs from multivariable analyses. Studies were conducted with differing matching criteria: age or age group, sex and telephone prefix or geographical location. Neal and Bloomfield conducted an unmatched study,<sup>26</sup> while Ikram et al.<sup>25</sup> calculated their crude OR with the total population being participants who had eaten poultry ( $n=81$  for both cases and controls) and not the total population interviewed ( $n=100$  for both cases and controls). As such, we recalculated the crude OR using 100 as the total populations for these groups. After

undergoing meta-analysis, the risk factor 'eating undercooked poultry' remained statistically significant (OR=3.88, 95%CI 2.75-5.47,  $I^2=0\%$ ), see Figure 2A.

Likewise, 'having pet chickens' remained a significant risk factor after meta-analysis (OR=3.29, 95%CI 2.12-5.10,  $I^2=0\%$ ), see Figure 2B. The meta-analysis for pet chickens as a risk factor included: keeping of live chickens, ownership of pet chickens, and ownership of domestic chickens aged less than six months. All three studies reported aORs; however, these were adjusted for different confounders. Cameron et al.<sup>23</sup> matched for age and sex, Stafford et al.<sup>11</sup> for age group only, and Tenkate and Stafford<sup>28</sup> matched for age, sex and location.

Conducting a meta-analysis of the risk factor 'eating poultry not cooked at home' presented some issues. Firstly, there were six risk factors that were included in this broad category: eating any chicken prepared at a sit-down restaurant, eating any chicken prepared at someone else's house, poultry eaten at a friend's house, restaurant-prepared chicken, chicken eaten at 'other' places, and eating chicken not cooked at home in the last three days. Two of the six risk factors combined

Figure 1: PRISMA flow diagram of systematic review steps.

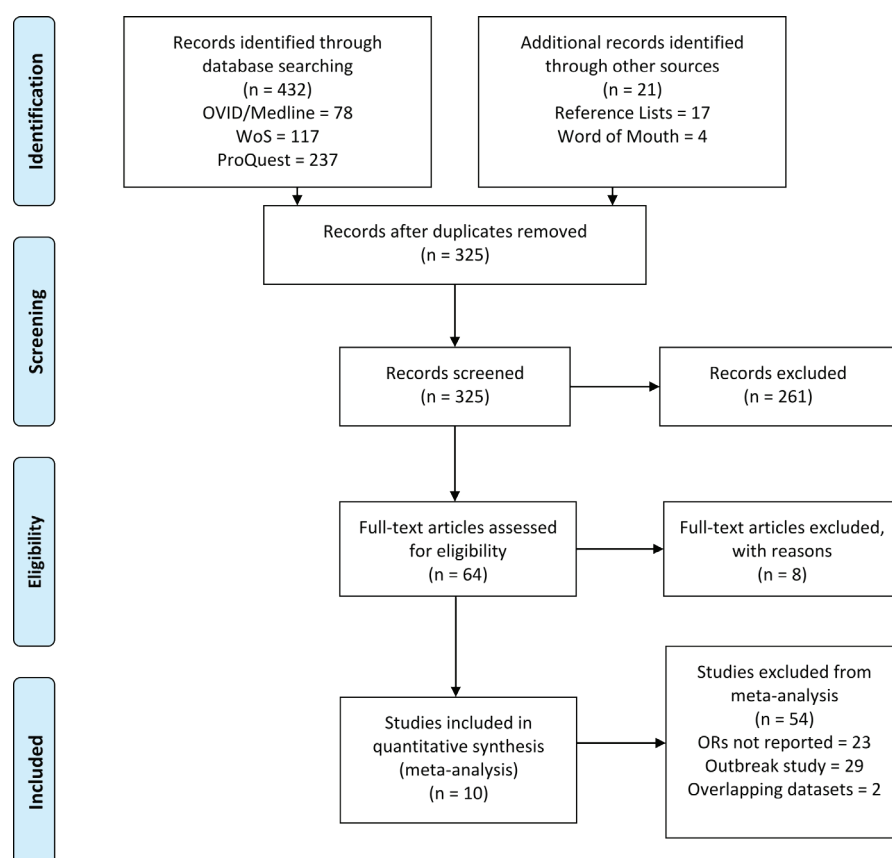


Table 1: Case-control studies of sporadic human campylobacteriosis in Australia and New Zealand from 1990 to 2016..

Author(s)	Year	Country	Cases	Controls	Age	Risk factors identified as statistically significant (OR*, 95%CI)	Adjustments	Limitations	Newcastle-Ottawa Scale Rating
McMahon & Mahmood <sup>21</sup>	1993	New Zealand	26	26	≥20 years	1. Contact with a sick person (OR=10.29, 95%CI=1.80–103.00)	N/A	1. Small study size (n=26 for each cases and controls) 2. Controls selected by nomination by cases or authors 3. Multivariable analysis not performed	7
Ikram et al. <sup>25</sup>	1994	New Zealand	100	100	All	1. Undercooked poultry (OR=4.94, 95%CI=1.03–23.62) 2. Eating poultry at a friend's house (OR=3.18, 95%CI=1.00–10.73) 3. Eating chicken at a barbecue (OR=3.00, 95%CI=0.99–9.34, p=0.03)	N/A	1. Focussed on Christchurch region – bias toward urban risk factors 2. Small study size (n=100 for each cases and controls) 3. Multivariable analysis not performed	5
Eberhart-Phillips et al. <sup>24</sup>	1997	New Zealand	621	621	All	1. Raw/undercooked chicken (aOR=3.71, 95%CI=2.24–6.13) 2. Chicken eaten in restaurants (aOR=3.53, 95%CI=2.17–5.72) 3. Chicken prepared at someone else's house (aOR=1.77, 95%CI=1.12–2.80) 4. Rainwater source for home water supply (aOR=3.11, 95%CI=1.30–7.41) 5. Puppy ownership (aOR=3.94, 95%CI=1.57–9.88) 6. Contact with calf faeces (aOR=4.40, 95%CI=1.34–14.39) 7. Unpasteurised milk (aOR=3.92, 95%CI=1.66–9.27)	Age group Sex Location (telephone prefix)	1. Social desirability bias when asking participants about kitchen hygiene practices	7
Neal & Bloomfield <sup>26</sup>	1997	New Zealand	55	55	≥15 years	1. Eating barbecued chicken (OR=10.6, 95%CI=1.0–105.6) (p=0.01 after adjusting for confounding, aOR and 95%CI not reported) 2. Eating undercooked chicken (OR=9.6, 95%CI=0.9–103.0) (p=0.04 after adjusting for confounding, aOR and 95%CI not reported) 3. Eating fast food (OR=2.6, 95%CI=1.1–6.1) (p=0.02 after adjusting for confounding, aOR and 95%CI not reported) 4. Overseas travel (OR=6.3, 95%CI=1.0–41.4)	Sex	1. Unpublished study 2. Outbreak investigation that turned into endemic disease investigation 3. aORs and associated 95%CI were not reported 4. Small study size (n=55 for each cases and controls) 5. Selection bias – different age profiles of cases and controls	2
Tenkate & Stafford <sup>28</sup>	2001	Australia	81	144	<3 years	1. Puppy ownership (aOR=16.58, 95%CI=3.73–73.65) 2. Chickens (as pets) (aOR=11.80, 95%CI=1.37–101.75) 3. Mayonnaise (aOR=4.13, 95%CI=1.61–10.59)	Age Sex Location (postcode)	1. Predominantly urban setting 2. Small number of cases (n=81)	7
Cameron, Ried, Worsley & Topping <sup>23</sup>	2004	Australia	172	169	1–5 years	1. Chickens (as pets) (aOR=4.5, 95%CI=1.5–14.0) 2. History of colon cancer in immediate family (aOR=1.9, 95%CI=1.1–3.3)	Age Sex	1. Recall bias 2. Focus of study was dietary habits in children diagnosed with campylobacteriosis rather than risk factors for infection	7
Baker, Wilson, McIntyre & McLean <sup>22</sup>	2005	New Zealand	50	50	All	None	Age Location (territorial local authority area)	1. Broad age range (<1–88 years) for small sample size 2. Student interviewers (n=11) 3. Small study size (n=50 for each cases and controls)	6
Stafford et al. <sup>11</sup>	2007	Australia	881	833	≥5 years	1. Eating undercooked chicken (aOR=4.7, 95%CI=2.6–8.4) 2. Eating offal (aOR=2.0, 95%CI=1.0–4.0) 3. Contact with chickens aged <6 months (aOR=12.4, 95%CI=2.6–59.3) 4. Contact with puppies aged <6 months (aOR=2.1, 95%CI=1.1–4.2)	Age Income Location (state)	1. Although a large study size, there were insufficient participant numbers to calculate 95%CI for population attributable risk percentages for all variables of interest in the multivariable logistic regression model (i.e. pet chickens aged <6 months old)	8
Unicomb et al. <sup>29</sup>	2008	Australia	354	593	≥5 years	1. Exposure to diarrheal illness (aOR=2.9, 95%CI=1.6–5.3) 2. Chicken from a restaurant (aOR=2.4, 95%CI=1.7–3.3) 3. Roast beef from a restaurant (aOR=2.4, 95%CI=1.1–5.4) 4. Eating 2 or more fast food meals a week (aOR=2.7, 95%CI=2.0–3.8) 5. Having a pet dog (aOR=1.5, 95%CI=1.1–2.1) 6. Overseas travel (aOR=7.5, 95%CI=2.5–23.0) 7. Swimming in a hot tub (aOR=2.7, 95%CI=1.1–7.0) 8. Swimming in a pond (aOR=2.2, 95%CI=1.1–4.5)	Age Sex	1. Selection bias of cases – higher proportion of severely ill cases included 2. Selection bias of controls – controls significantly older than cases	6
Stephens et al. <sup>27</sup>	2009	Australia	138	134	0–4 years	1. Sucking fingers, thumbs or a dummy (aOR=2.5, 95%CI=1.4–4.3) 2. Pet dog (aOR=1.1, 95%CI=1.0–1.3) 3. Sausages (aOR=2.0, 95%CI=1.2–3.2)	Age Income Location (state)	1. Unpublished study	8

Note: \*OR = crude odds ratio; aOR = adjusted odds ratio



in this analysis were crude ORs, matched for age and sex.<sup>21,25</sup> The other four analyses reported aORs and were matched on slightly different criteria: two from Eberhart-Phillips<sup>24</sup> were matched for age, sex and telephone prefix; with Unicomb et al.<sup>29</sup> matching for age and sex only; and Baker, Wilson, McIntyre and McLean<sup>22</sup> matching for age group and Territorial Local Authority area. As with the 'eating undercooked poultry' meta-analysis, we recalculated the crude OR for Ikram et al.<sup>25</sup> using 100 as the total populations for cases and controls.

Eberhart-Phillips et al.<sup>24</sup> included two of the aforementioned risk factors (chicken prepared at a sit-down restaurant and chicken prepared at someone else's house) in a multivariable analysis, with both found to be independently significant. Meta-analyses were conducted including either one of the risk factors from this study for comparison. Both meta-analyses showed statistical significance with low-to-no heterogeneity (OR=2.03, 95%CI 1.57-2.63, I<sup>2</sup>=0%; OR=2.85, 95%CI 2.01-4.05, I<sup>2</sup>=23.2%). The forest plot including the risk factor 'chicken prepared at someone else's house' has been included (Figure 2C), with the forest plot including 'chicken prepared at a sit-down restaurant' available as Supplementary File 2.

Five of the analyses identified an elevated OR for overseas travel, with four of these ORs considered significant. Each of these studies looked specifically at overseas travel except for Tenkate and Stafford,<sup>28</sup> which looked at the variable 'travel – intra/interstate, overseas'. After meta-analysis (see Supplementary File 3), this risk factor remained significant (OR=5.55, 95%CI 3.20-9.63, I<sup>2</sup>=0%).

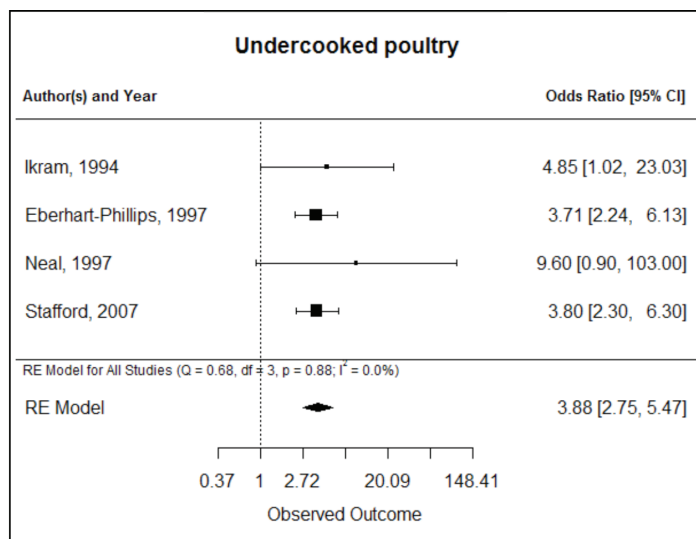
## Discussion

This meta-analysis identified four risk factors as statistically significant for campylobacteriosis in Australia and New Zealand: eating undercooked poultry; having pet chickens; eating poultry not cooked at home; and travelling overseas. These risk factors are comparable to those identified in overseas studies as being significant risk factors for human campylobacteriosis, especially in other high-income countries.

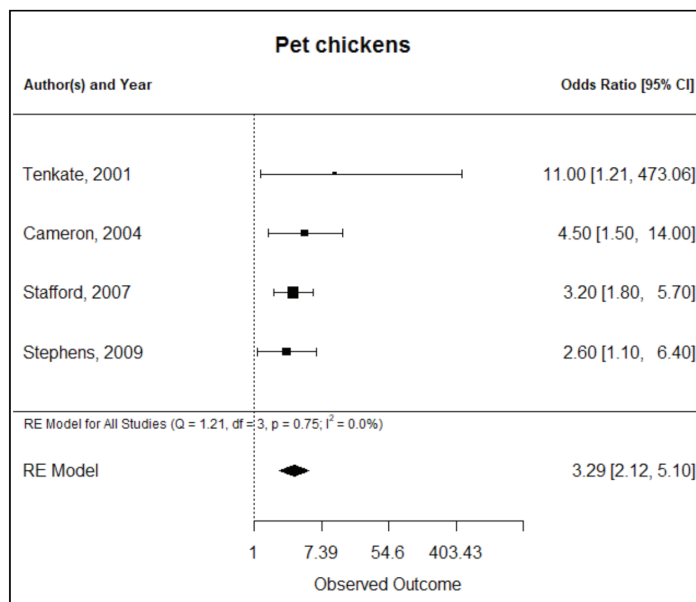
Zoonotic exposures were the most common risk factor identified in studies targeting young children. This is not surprising considering the behaviours and habits of this age group, which is further highlighted in the

Figure 2: Forest plots for meta-analyses of (A) eating undercooked poultry, (B) having pet chickens, and (C) eating poultry not cooked at home as risk factors for campylobacteriosis.

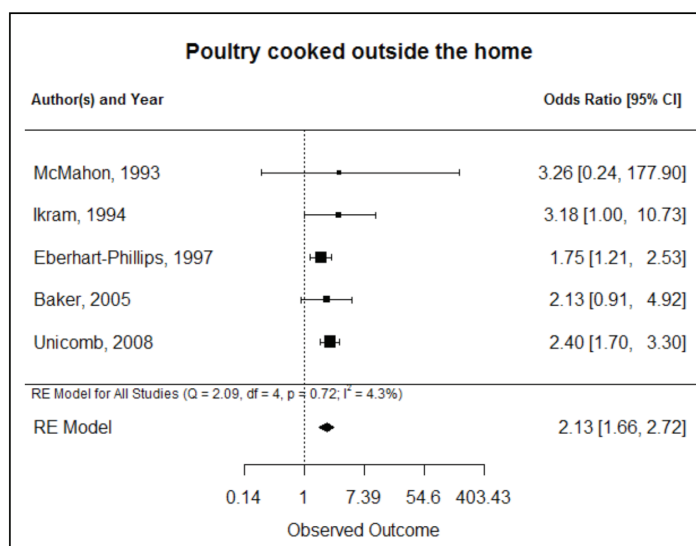
A



B



C



identification of “sucking fingers, thumbs or a dummy” as another significant risk factor in one study.<sup>27</sup> The consumption of chicken or poultry meat was not identified as a significant risk factor in any of the analyses for this age group, although it was the most commonly identified risk factor in studies that excluded young children or looked at risk factors across all ages. This may be a result of inadequate power to detect an effect; however, these data may indicate that environmental contamination and zoonotic transmission may be particularly important in young children in Australia and New Zealand, which is consistent with findings in other high-income settings.<sup>33,34</sup> These findings clearly indicate that zoonotic exposures are an important risk for human infections, especially in young children, which requires more public awareness.

Much like salmonellosis, campylobacteriosis is primarily considered a foodborne illness. This leads to prevention strategies focusing on food safety and kitchen hygiene, with risks associated with zoonotic exposure only highlighted when visiting specialist facilities such as petting zoos or small animal farms. While these facilities do still pose a risk for infection, domestic dogs have been shown as a far more prevalent risk factor globally.<sup>32,34</sup> Basic hand hygiene and preventing pet dogs from licking the hands and faces of young children is important for reducing zoonotic infections such as campylobacteriosis in the home environment.

Eating poultry not cooked at home is a risk factor that is reported regularly in studies on campylobacteriosis. Given that chicken is commonly eaten in Australian households, a possible explanation is that people acquiring *Campylobacter* from poultry eaten outside of the home tend to cook it less within the home and may have lower immunity to *Campylobacter*.<sup>35</sup> There is limited literature on immunity to campylobacteriosis, but those available demonstrate that more frequent exposure to *Campylobacter* results in less illness.<sup>35</sup> Cawthraw et al.<sup>36</sup> investigated antibody levels in short- and long-term poultry abattoir workers in Sweden. This study found that regular, long-term exposure to *Campylobacter* results in antibodies that appear to reduce susceptibility to illness, so it follows that regularly cooking chicken at home may also result in protective antibodies. There have been numerous studies conducted in other high-income countries comparing clinically isolated *Campylobacter*

strains to those found in potential environmental and animal sources. Petersen et al.<sup>37</sup> identified a significant overlap in serotypes isolated from human samples and those found in broiler chicken flocks, and determined that wildlife strains (including those isolated from various wild birds and mammals) were of limited importance as a reservoir for human infection. Duim, Wassenaar, Rigter and Wagenaar<sup>38</sup> found the same genotypes in human- and poultry-derived isolates, with others also showing similarities between human and poultry isolates.<sup>39</sup> These studies support our findings that poultry is a primary source of human *Campylobacter* infection in the Australian and New Zealand populations. They also highlight food as being a more prominent source of infection than environmental sources. As the three studies do not provide information on human cases' ages, we cannot determine whether there were differences in young children consistent with greater environmental exposure.

A major study in the Netherlands used genotype-based source attribution for human campylobacteriosis.<sup>40</sup> Using a combined case-control and source attribution analysis, they found that most human infections were derived from chicken (66.2%), followed by cattle (20.7%), environment (10.1%), sheep (2.5%) and pigs (0.3%). Consumption of chicken was considered the primary risk factor for chicken-associated campylobacteriosis, further reinforcing that this is a major source of infection worldwide.

Two of the 10 case-control studies included ‘contact with a sick person’ as a potential risk factor and both studies identified a statistically significant risk. McMahon and Mahmood<sup>21</sup> defined this risk factor as contact with an ill person in the seven days prior to onset of illness for cases (or in the seven days prior to interview for controls). Unicomb et al.<sup>29</sup> investigated household exposure to diarrhoeal illness in the four weeks prior to onset of illness for cases (or four weeks prior to interview for controls). It is possible that these contacts shared a common source of infection and person-to-person transmission did not occur in these instances, as neither study explicitly excluded this.

There were some limitations to this meta-analysis. Two of the case-control studies only conducted a univariable analysis of potential risk factors, and these risk factors may be affected by confounding. The meta-analyses presented the further complexity

of heterogeneity. Studies were assessed for heterogeneity, and we demonstrated high levels in two of the three studies into having pet dogs as a risk factor. The third study showed low heterogeneity but was not significant. These meta-analyses were also affected by most studies including only a small number of participants.

Some of the studies identified in this meta-analysis involved a small number of participants. As a result, not all relevant risk factors may have odds ratios reported in enough studies to be included in the meta-analysis. One study failed to identify any risk factors as significant, possibly due to insufficient power (n=50 for each of cases and controls).<sup>22</sup> These small study numbers may also have resulted in an overrepresentation of risk factors that are less common exposures.

Another limitation is that few studies (2/10) investigated what is considered an important source of infection globally – consumption of raw milk. As the sale of raw milk is illegal in Australia, it was not a priority for Australian studies. Similarly, offal is considered an important source of human *Campylobacter* infection globally but appeared significant in only one of the eight studies that investigated this item. The population attributable risk for *Campylobacter* infection from offal in Australia has been calculated at 2.1% (95%CI 0.0–4.9%), so it is not considered a major source.<sup>11</sup> These facts highlight the need for locally relevant risk factors to be assessed.

It is well documented that consumption of chicken is a major source of campylobacteriosis, but this meta-analysis clearly shows a need for more research into non-food-related risk factors. We identified eating undercooked poultry, having pet chickens, eating chicken not cooked at home and overseas travel as major risk factors for campylobacteriosis in Australia and New Zealand. More research should be done into the risk of having pet dogs and *Campylobacter* infection, especially around young children. Likewise, person-to-person transmission should also be included in future studies investigating causes of human campylobacteriosis. The risk factors identified in this meta-analysis as being major contributors to sporadic human campylobacteriosis in Australia and New Zealand will inform future studies that combine epidemiology and genomics to identify contemporary and locally relevant risk factors for the disease.

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## References

- Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global epidemiology of Campylobacter infection. *Clin Microbiol Rev.* 2015;28(3):687-720.
- Kirk M, Ford L, Glass K, Hall G. Foodborne illness, Australia, circa 2000 and circa 2010. *Emerg Infect Dis.* 2014;20(11):1857-64.
- Australian Department of Health. *National Notifiable Diseases Surveillance System* [Internet]. Canberra (AUST): Government of Australia; 2019 [cited 2019 Feb 01]. Available from: <http://www9.health.gov.au/cda/source/cda-index.cfm>
- The Institute of Environmental Science and Research. *Notifiable Diseases in New Zealand: Annual Report 2016*. Wellington (NZ): ESR; 2017.
- Sears A, Baker MG, Wilson N, Marshall JC, Müllner P, Campbell DM, et al. Marked Campylobacteriosis decline after interventions aimed at poultry, New Zealand. *Emerg Infect Dis.* 2011;17(6):1007.
- Hall G, Yohannes K, Raupach J, Becker N, Kirk MD. Estimating community incidence of Salmonella, Campylobacter, and Shiga toxin-producing Escherichia coli infections, Australia. *Emerg Infect Dis.* 2008;14(10):1601-9.
- Cressey P, Lake R. *Estimated Incidence of Foodborne Illness in New Zealand: Application of Overseas Models and Multipliers*. Wellington (NZ): Institute of Environmental Science and Research; 2011.
- Vally H, Glass K, Ford L, Hall G, Kirk MD, Shadbolt C, et al. Proportion of illness acquired by foodborne transmission for nine enteric pathogens in Australia: An expert elicitation. *Foodborne Pathog Dis.* 2014;11(9):727-33.
- Heymann DL. *Control of Communicable Diseases Manual*. 19th ed. Washington (DC): American Public Health Association; 2008.
- Olson CK, Ethelberg S, van Pelt W, Tauxe RV. Epidemiology of Campylobacter jejuni infections in industrialized nations. In: Nachamkin I, Szymanski CM, Blaser MJ, editors. *Campylobacter*. 3rd ed. Washington (DC): American Society for Microbiology; 2008.
- Stafford Russell J, Schluter PJ, Kirk MD, Wilson AJ, Unicomb L, Ashbolt R, et al. A multi-centre prospective case-control study of Campylobacter infection in persons aged 5 years and older in Australia. *Epidemiol Infect.* 2007;135(6):978-88.
- Unicomb LE, Fullerton KE, Kirk MD, Stafford RJ. Outbreaks of Campylobacteriosis in Australia, 2001 to 2006. *Foodborne Pathog Dis.* 2009;6(10):1241-50.
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA.* 2000;283(15):2008-12.
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses* [Internet]. Ottawa (CAN): The Ottawa Hospital Research Institute; 2019 [cited 2019]. Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J.* 2003;327(7414):557-60.
- Viechtbauer W. The metafor package: A meta-analysis package for R. *J Stat Softw* [serial on the Internet]. 2010 [cited 2018 Oct 10];36(3):1-48. Available from: <http://www.metafor-project.org/doku.php>
- Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Random-effects model. In: Borenstein M, et al. *Introduction to Meta-Analysis*. Chichester (UK): Wiley; 2009. p. 69-75.
- Viechtbauer W. Conducting meta-analyses in R with the metafor Package. *J Stat Softw.* 2010;36(3):1-48.
- Halasa T, Nielsen M, Whist AC, Østerås O. Meta-analysis of dry cow management for dairy cattle. Part 2. Cure of existing intramammary infections. *J Dairy Sci.* 2009;92(7):3150-7.
- McMahon D-J, Mahmood F. Endemic Campylobacter in South Auckland. *Commun Dis NZ.* 1993;93:70-2.
- Baker MG, Wilson N, McIntyre M, McLean M. Findings and methodological lessons from a small case-control study into campylobacteriosis in Wellington. *NZ Med J.* 2005;118(1220):U1622.
- Cameron S, Ried K, Worsley A, Topping D. Consumption of foods by young children with diagnosed Campylobacter infection – a pilot case-control study. *Public Health Nutr.* 2004;7(1):85-9.
- Eberhart-Phillips J, Walker N, Garrett N, Bell D, Sinclair D, Rainger W, et al. Campylobacteriosis in New Zealand: Results of a case-control study. *J Epidemiol Community Health.* 1997;51(6):686-91.
- Ikram R, Chambers S, Mitchell P, Brieseman MA, Ikam OH. A case control study to determine risk factors for campylobacter infection in Christchurch in the summer of 1992-3. *NZ Med J.* 1994;107(988):430-2.
- Neal G, Bloomfield A. A Case Control Study of Campylobacter Infections Notified to Auckland Healthcare During a 25 Day Period in October/November 1996. Unpublished Observations. 1997.
- Stephens N, Stafford RJ, Fullerton KE, Ashbolt R, Kirk MD, Gregory J, et al. Sporadic Campylobacter Infection in Children Aged 0-4 Years in Australia: A Multi-centre prospective Case-control Study. Unpublished Observations. 2009.
- Tenkate TD, Stafford RJ. Risk factors for campylobacter infection in infants and young children: A matched case-control study. *Epidemiol Infect.* 2001;127(3):399-404.
- Unicomb LE, Dalton CB, Gilbert GL, Becker NG, Patel MS. Age-specific risk factors for sporadic Campylobacter infection in regional Australia. *Foodborne Pathog Dis.* 2008;5(1):79-85.
- Doyle MP. Association of Campylobacter jejuni with laying hens and eggs. *Appl Environ Microbiol.* 1984;47(3):533-6.
- Graham C, Whyte R, Gilpin BJ, Cornelius A, Hudson JA, Morrison D, et al. Outbreak of campylobacteriosis following pre-cooked sausage consumption. *Aust NZ J Public Health.* 2005;29(6):507-10.
- Kapperud G, Skjerve E, Bean NH, Ostroff SM, Lassen J. Risk factors for sporadic Campylobacter infections: Results of a case-control study in southeastern Norway. *J Clin Microbiol.* 1992;30(12):3117-21.
- Domingues AR, Pires SM, Halasa T, Hald T. Source attribution of human campylobacteriosis using a meta-analysis of case-control studies of sporadic infections. *Epidemiol Infect.* 2012;140(06):970-81.
- Carrique-Mas J, Andersson Y, Hjertqvist M, Svensson Å, Torner A, Giesecke J. Risk factors for domestic sporadic campylobacteriosis among young children in Sweden. *Scand J Infect Dis.* 2005;37(2):101-10.
- Evers EG, Van Der Fels-Klerx HJ, Nauta MJ, Schijven JF, Havelaar AH. Campylobacter source attribution by exposure assessment. *Int J Risk Assess Manag.* 2008;8(1-2):174-90.
- Cawthraw SA, Lind L, Kaijser B, Newell DG. Antibodies, directed towards Campylobacter jejuni antigens, in sera from poultry abattoir workers. *Clin Exp Immunol.* 2000;122(1):55-60.
- Petersen L, Nielsen EM, Engberg J, On SLW, Dietz HH. Comparison of genotypes and serotypes of Campylobacter jejuni isolated from Danish wild mammals and birds and from broiler flocks and humans. *Appl Environ Microbiol.* 2001;67(7):3115-21.
- Duim B, Wassenaar TM, Rigter A, Wagenaar J. High-resolution genotyping of Campylobacter strains isolated from poultry and humans with amplified fragment length polymorphism fingerprinting. *Appl Environ Microbiol.* 1999;65(6):2369-75.
- Wu TL, Su LH, Chia JH, Kao TM, Chiu CH, Kuo AJ, et al. Molecular epidemiology of nalidixic acid-resistant campylobacter isolates from humans and poultry by pulsed-field gel electrophoresis and flagellin gene analysis. *Epidemiol Infect.* 2002;129(1):227-31.
- Mughini Gras L, Smid JH, Wagenaar JA, de Boer AG, Havelaar AH, Friesema IHM, et al. Risk factors for campylobacteriosis of chicken, ruminant, and environmental origin: A combined case-control and source attribution analysis. *PLoS One.* 2012;7(8):e42599.

## Supporting Information

Additional supporting information may be found in the online version of this article:

**Supplementary File 1:** Forest plots for meta-analyses of (A) having pet dogs, (B) having pet dogs (limited to “young children”), and (C) having pet dogs aged less than 6 months as risk factors for campylobacteriosis.

**Supplementary File 2:** Forest plot for meta-analysis of “eating poultry not cooked at home” as a risk factor for campylobacteriosis, including only the risk factor “any chicken prepared at a sit-down restaurant” from Eberhart-Phillips, 1997.

**Supplementary File 3:** Forest plot for meta-analysis of overseas travel.