

Examining the epidemiology of campylobacteriosis in Australia

A thesis submitted for the degree of Doctor of Philosophy of the Australian National University

Cameron Robert Macquarie Moffatt

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“He has in his make-up two essential elements—common sense and the will to work ... in collecting [facts] he is diligent, patient, careful, thorough and unbiased ... he avoids needless or obfuscating high mathematics and formulae ... he does not twist the facts... He remains broad-minded and open-minded ... He is humble in his ignorance but bold in his search for truth” Leslie Leon Lumsden (1875–1946).

Declaration – thesis by compilation

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University. The exceptions relate to multi-author papers incorporated in the Thesis where my contributions have been specified under the Statements of Contributions that precede each of the relevant chapters.

A handwritten signature in black ink, appearing to read 'C. Moffatt', is written over a horizontal line. The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Cameron Moffatt

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Abstract

Introduction.

Infection with *Campylobacter* spp. causes considerable disease burden in Australia. Despite this impact, a focused examination of the epidemiology of campylobacteriosis in Australia has been lacking. Disease incidence, outbreak potential and outcomes such as hospitalisation, represent key themes upon which the epidemiology of infectious pathogen can be assessed. Examination of these themes addresses gaps in epidemiological understanding, helping to inform prevention and control efforts. The initial thesis chapter provides detail on microbiological, clinical and epidemiological aspects of *Campylobacter* infection. Each theme is then separately addressed through a chapter that includes one or more studies presented as published manuscripts. These chapters also comprise a preface with further background, the research aim(s), study rationale and methodological considerations. A concluding chapter considers the themes through a discussion of the relationship between increasing age and *Campylobacter*-associated risk.

Methods.

Incidence. The aim was to describe and assess incidence trends for campylobacteriosis from 1998 to 2013, using national surveillance data. Negative binomial regression was used to estimate incidence rate ratios (IRRs) for gender, season, state and trend over time by age-group. **Outbreaks.** The aim was to describe the epidemiology of *Campylobacter* outbreaks in Australia using national outbreak data. Descriptive analyses were used to examine outbreak characteristics, including transmission routes and strength of evidence. An additional study describing an outbreak investigation that incorporated whole genome sequencing is included. **Hospitalisation.** The aims included quantifying *Campylobacter*-associated hospitalisations, describing their clinical characteristics, and examining factors associated with inpatient

investigation and management. Data from 2004 to 2013 were obtained from Australian Capital Territory (ACT) public hospital administrative and laboratory datasets. Morbidity coding sensitivity was calculated to assess hospital underreporting, with descriptive statistics being used to examine clinical and epidemiological characteristics. Factors associated with blood culturing, bacteraemia, antibiotic treatment and non-susceptibility of isolates to antimicrobials were assessed using multivariable logistic regression.

Results.

Incidence. The study included 245,023 *Campylobacter* notifications. Incidence among males was significantly higher (IRR 1.20, 95% confidence interval (CI) 1.18-1.21), and a distinct seasonality was demonstrated in spring (IRR 1.18, 95% CI 1.16-1.20) and summer (IRR 1.17, 95% CI 1.16-1.19). Age-specific incidence trends showed declines in those <40 years and concurrent increases among older age-groups, particularly those >70 years (IRR 1.75, 95% CI 1.63–1.88). **Outbreaks.** From 2001 to 2016, 84 *Campylobacter* outbreaks were identified in Australia. Of these, 61% (51/84) were foodborne, with *Campylobacter* responsible for 2.4% (51/2083) of all documented foodborne outbreaks. There was no increase in outbreaks over time but the proportion of foodborne outbreaks involving poultry-liver increased ($p=0.04$). Aged-care facilities (ACFs) were the most common setting, accounting for 26% (22/84) of outbreaks and a quarter of total outbreak-associated cases (252/1042), including 17 hospitalisations and three deaths. Twenty-seven percent (23/84) of outbreaks had an unknown transmission route, including 10 ACF outbreaks. **Hospitalisation.** There were 685 *Campylobacter*-associated hospitalisations, with a mean annual hospitalisation rate for the ACT of 13.6%. The sensitivity of morbidity coding among *Campylobacter*-associated hospitalisations was 52.8% (95% CI, 48.9-56.7%). The median (M) age of hospitalised cases was 38.4 years and was significantly higher than non-hospitalised community cases ($M=31.0$, $p<0.001$). Age-specific admission rates were higher for females, while for both sexes the

highest hospitalisation rates were observed in those ≥ 60 years. Comorbidities were present in 34.5% (237/685) of people admitted, with these patients being older and more likely to experience generalised complications, including dehydration, hypotension and renal impairment (all $p < 0.001$). Bacteraemia and acute kidney injury were observed in 4.1% (28/685) and 3.6% (23/685) of people admitted, while inpatient mortality was low (0.15%). *Campylobacter* bacteraemia was estimated at 0.71 cases per 100,000 population per year. Half of *Campylobacter*-associated hospitalisations (333/685) had blood cultures performed. Factors associated with bacteraemia included liver disease (adjusted Odds Ratio (aOR) 48.89, 95% CI 7.03-340.22, $p < 0.001$), Haematology unit admission (aOR 14.67, 95% CI 2.99-72.07, $p = 0.001$) and age 70-79 years (aOR 4.93, 95% CI 1.57-15.49). Antibiotics were provided to one-third of admissions (219/685), with treatment rates increasing over time ($p < 0.05$). Factors associated with antibiotic treatment included Gastroenterology unit admission (aOR 3.75, 95% CI 1.95-7.20, $p < 0.001$), blood collection for culture (aOR 2.76, 95% CI 1.79-4.26, $p < 0.001$) and age 40-49 years (aOR 2.34, 95% CI 1.14-4.79, $p = 0.02$). Increasing non-susceptibility of isolates over time was observed ($p = 0.01$). This was associated with overseas travel (aOR 11.80 95% CI 3.18-43.83, $p < 0.001$) and negatively associated with tachycardia (aOR 0.48, 95%CI 0.26-0.88, $p = 0.02$), suggesting a healthy traveller effect.

Conclusion. Australia has experienced high and sustained rates of campylobacteriosis, with increasing incidence predicted among older age-groups. Despite the high incidence, outbreaks have been demonstrated to occur infrequently. Conversely, hospitalisations are significantly underestimated. Further work is required to understand hospitalisation, including examination of age and comorbidity as predictors. *Campylobacter* generates a significant public health and clinical burden, with risk of infection and poor health outcomes highest among older Australians.

Table of Contents

Chapter 1 – An overview of <i>Campylobacter</i> spp. as a human pathogen	1
Introduction.....	1
Microbiology.....	1
Reservoirs and routes of transmission for infection.....	2
Pathogenesis and clinical presentation	4
Diagnosis and treatment.....	5
Epidemiology and risk factors	6
Outbreaks	7
References.....	9
Chapter 2 – Examining the incidence of infection with <i>Campylobacter</i> spp. in Australia.....	18
References.....	22
Manuscript 1 – Incidence theme	24
Chapter 3 – Outbreaks of campylobacteriosis infection in Australia	33
References.....	39
Manuscript 2 - Outbreak theme.....	42
Manuscript 3 – Outbreak theme.....	50
Chapter 4 <i>Campylobacter</i> -associated hospitalisation	58
References.....	68
Manuscript 4 – Hospitalisation theme.....	72
Manuscript 6 – Hospitalisation theme.....	94
Chapter 5 - Discussion	98

References	106
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Chapter 1 – An overview of *Campylobacter* spp. as a human pathogen

Introduction

Campylobacter spp. are an internationally leading cause of gastroenteritis, resulting in an estimated 96 million cases of foodborne disease each year [1]. The majority of these infections are caused by two species *Campylobacter jejuni* and *C. coli*. In this chapter I provide a brief review of campylobacteriosis, with an emphasis on disease occurrence in high income settings [2], such as Australia, Canada, the European Union (EU), Japan, New Zealand (NZ), the United Kingdom (UK) and the United States (US). In this background review I include descriptions of the microbiology, reservoirs and transmission routes, pathogenesis and clinical features, diagnosis and treatment, epidemiological burden and outbreaks caused by *Campylobacter* spp.

Microbiology

The genus *Campylobacter* consists of no less than 33 species of gram-negative, non-spore forming, predominantly motile microorganisms [3, 4]. The two species causing the majority of human disease are *Campylobacter jejuni* and *C. coli*. [5]. A number of other species can cause gastrointestinal and/or extra-intestinal disease in humans, including *C. concisus*, *C. fetus*, *C. lari*, *C. upsaliensis* and *C. ureolyticus* but the methods routinely employed in most clinical laboratories do not favour recovery of these species [5]. As more can be inferred about the contributions of *C. jejuni* and *C. coli* to human illness, these species will form the basis upon which I describe *Campylobacter*'s role as a human pathogen.

Campylobacter spp. are nutritionally fastidious organisms, with an unusual sensitivity to environmental stress [6]. While many foodborne enteric pathogens are considered relatively robust, the physiology of *Campylobacter* spp. contrasts with their capacity to navigate through the food chain and wider environment. In order to proliferate *Campylobacter* require

microaerophilic conditions and a narrow temperature range of between 37°C and 42°C (optimally 42°C) [6, 7]. Given these requirements, *Campylobacter* spp. are incapable of replicating at temperatures typically associated with food storage [6]. Key environmental stressors impacting *Campylobacter*'s ability to survive on foods include a susceptibility to cold and heat shock, being readily inactivated by freezing and cooking, desiccation (drying) and both osmotic and pH stress [6, 7]. Consequently, it becomes difficult to reconcile *Campylobacter*'s role as a leading foodborne pathogen with its relative fragility. Survival of the organism is undoubtedly facilitated through a complex interaction between the organism, its hosts and environment, including adaptive survival mechanisms and virulence factors [7], the popularity of poultry meat as a protein source, combined with high levels of contamination [8, 9] and a lack of consumer awareness of disease and transmission risk [10, 11]

Reservoirs and routes of transmission for infection

The primary reservoir and main amplification site for *Campylobacter* spp. are the intestinal tracts of warm-blooded animals, in particular poultry and wild bird species but also livestock animals including cattle, sheep and pigs [12]. Source attribution is a term used to describe methods of linking human disease back to putative sources or reservoirs of infection such as animals, with approaches evolving from epidemiological studies including outbreak investigation and case control studies, to statistical modelling of microbial subtyping and population genetics data [13]. While epidemiological approaches can identify factors e.g. chicken meat consumption [14], source attribution modelling links human *Campylobacter* isolates to those derived from a variety of sources. These models have provided compelling evidence that poultry (specifically chickens), are the major reservoir for *Campylobacter* spp. in high-income settings, with ruminants (cattle and sheep) also being consistently implicated in a substantial proportion of cases [15]. The relative contributions of these reservoirs can

vary between settings because of cultural, food consumption and primary production differences [16].

Most *Campylobacter* infections are regarded as being transmitted via food. For poultry, contamination and colonisation of broilers with *Campylobacter* spp. at the farm level leads to transmission throughout the poultry production and processing chain, with retail poultry meat being heavily contaminated [9]. As *Campylobacter* is largely a surface contaminant of poultry meat [17], human infection most commonly occurs via cross contamination, either directly from raw to cooked chicken or another component of a meal or indirectly via kitchen utensils or hands that have contacted raw meat or contaminated packaging [18]. For domestic ruminants disease risk varies by setting, with non-foodborne transmission and environmental contamination identified as being important in Canada [19, 20]. Unpasteurised dairy products derived from ruminant species are however an important source, leading to frequent outbreaks in settings like the US, where raw milk consumption is more common [21].

Water can be an important source of campylobacteriosis with evidence from outbreak investigations demonstrating the role of surface and groundwater contamination [22]. Some *Campylobacter* appear able to survive in water, with their persistence favoured by low temperature, an absence of sunlight and low numbers of indigenous microbiota [23]. Further adaptations such as biofilm formation, a viable but non-culturable state, and interactions with other microorganisms may also assist their survival [24]. Surface waters such as reservoirs, lakes and rivers become contaminated with *Campylobacter* spp. as a result of animal faeces, sewage effluent and agricultural run-off [23]. In both the Netherlands and NZ, recent studies have identified wild birds and farmed poultry as reservoirs responsible for surface water contamination [25, 26]. Groundwater, including private water sources such as wells, can also become contaminated through septic leakage, wastewater intrusion or cross-connection into drinking water distribution systems [23]. In addition, recreational water activity such as

swimming in natural water bodies like rivers, lakes and streams has also been identified as a risk factor for campylobacteriosis in settings including Canada and Finland [27, 28].

In addition to food production animals, case control and attribution studies have also identified companion animals such as dogs to be potential reservoirs for *Campylobacter* spp., with puppy ownership identified as a risk factor for human campylobacteriosis [29, 30].

While uncommon, person-to-person transmission may also occur, with a New Zealand study of campylobacteriosis transmission concluding that 4% of cases were transmitted via that route [31].

Pathogenesis and clinical presentation

Campylobacteriosis most typically presents as an acute, self-limiting gastrointestinal illness characterised by diarrhoea, fever and abdominal pain [32]. Nausea and vomiting may also be reported [33]. While the onset of diarrhoea and abdominal pain is often abrupt, some cases may experience a prodromal phase of illness involving non-specific signs and symptoms such as fever, headaches and malaise lasting >24 hours [34]. The spectrum of diarrhoea ranges from loose stools, through profuse watery diarrhoea to bloody stools [35]. The occurrence of either bloody diarrhoea or vomiting are indicative of more severe disease [36]. The incubation period is typically between 2 to 5 days, with symptoms persisting from between a few days to two weeks [37]. The range for incubation is likely influenced by the size of the inoculum, with the infective dose for *C. jejuni* thought to be as low as 500 bacteria [38].

The pathogenesis of campylobacteriosis is complex with infection aided by mechanisms including flagella-mediated motility, adherence to the intestinal epithelium, invasive capability, toxin production and chemotactic factors [39]. After ingestion, *C. jejuni* first colonise the mucus lining of the small intestine, before moving to the large intestine as infection progresses [38]. Following mucosal colonisation, *C. jejuni* adhere to the intestinal

epithelial cells, before breaching this barrier through direct cell invasion or by passing between tight cell junctions [40]. *C. jejuni* then either reinvade the epithelial cells or are taken up by macrophages, with these interactions resulting in the release of chemokines and cytokines that contribute to both inflammatory diarrhoea and ultimately clearance of the infection [40].

While campylobacteriosis overwhelmingly presents as an enterocolitis, a number of uncommon local and extra-intestinal complications have been recognised. Localised complications can include appendicitis [41], cholecystitis [42] and toxic megacolon [43]. Among extra-intestinal complications, bacteraemia is most commonly recognised but occurs in <1% of patients with *Campylobacter* enterocolitis [32]. Other extra-intestinal complications include cellulitis [44], spontaneous abortion [45], myopericarditis [46], pancreatitis [47] and osteomyelitis [48].

Campylobacter infection can also result in an increased risk for development of post-infectious sequelae including Guillain-Barré Syndrome (GBS), a neurological disease that causes ascending paralysis; reactive arthritis (ReA), an arthropathy characterised by sterile joint inflammation and irritable bowel syndrome (IBS), a functional disorder of the gastrointestinal tract [49-51]. Antecedent *C. jejuni* enteritis is linked to around 30% of all GBS cases making it the most commonly identified bacterial cause of this syndrome [50]. ReA is reported to occur in between 1 to 5% of persons previously infected with *Campylobacter* spp. [49], while the prevalence of IBS following campylobacteriosis is estimated at 12% [52].

Diagnosis and treatment

Laboratory diagnosis for *Campylobacter* infection has traditionally been established by culture of clinical samples, most often faecal specimens [33]. More recently, culture-

independent testing methods have emerged as an alternative to culture, providing greater test sensitivity and same-day results, although the absence of an isolate limits additional characterisation including antimicrobial susceptibility testing [33]. Most infections do not require antimicrobial treatment, instead maintenance of hydration and electrolyte balance are the main focus of patient management [32]. Antibiotics may be recommended for some patients, including those with prolonged or severe symptoms, systemic infections, and those within high-risk groups including the elderly or immuno-compromised [35].

Fluoroquinolones or macrolide antibiotics are generally prescribed, although variations in antibiotic guidelines exist between high-income countries [53-55]. These variations can be attributed to increasing fluoroquinolone resistance in *Campylobacter* isolates, particularly in North America and Europe [56, 57].

Epidemiology and risk factors

Males have been consistently shown to have higher rates of campylobacteriosis, with this extending across most age-groupings [56, 58]. Overall age distribution is generally described as being bimodal, with prominent incidence peaks observed among infants and children <5 years of age, and again in younger adults, ranging between 15-45 years of age [59, 60].

Hospitalisation occurs in around 10% of cases [60, 61], while mortality is low with a reported case fatality rate of 0.1% [62]. Most deaths have been reported as occurring in older adults or those with underlying comorbidities [62, 63].

In high-income settings, including Australia, the EU, NZ and the US, *Campylobacter* spp. are the most frequently reported cause of bacterial gastroenteritis [64-67]. A recent review concluded that the incidence of infection in North America, Europe and Australia has increased over the last decade [68]. Despite these reported increases, considerable intercountry variations in incidence rates exist. Higher rates are reported in NZ (135.4 cases per 100,000 population) and Australia (101.8 cases per 100,000 population) [65, 66],

compared to the EU (64.8 cases per 100,000 population) [64] while rates are considerably lower in the US (19.5 cases per 100,000 population [67]. These differences might be attributed to population profiles, laboratory detection methods, surveillance systems, food practices and the relative importance of different reservoirs and transmission routes between countries [68].

Numerous cases control studies have been conducted to identify risk factors and transmission routes associated with sporadic campylobacteriosis. Common risk factors identified have included poultry meat consumption [30, 69-71], consumption or contact with untreated water [71-73] and contact with animals [30, 71-73]. To better synthesise this evidence, meta-analyses of case control studies examining risk factors for sporadic campylobacteriosis have been undertaken. These analyses have generated largely comparable findings, including the importance of overseas travel, animal contact, exposure through environmental sources, host factors such as pre-existing chronic conditions, recent antacid use and the consumption of a variety of foods, including poultry meat [14, 74].

Further assessment of disease burden can be made through calculation of disability-adjusted life years (DALY), a measure of impact of years lived with disability and of years of life lost due to premature mortality [75]. Campylobacteriosis burden varies considerably between regions, reflecting not only differences in regional incidence but also variations in the methods used in their calculation. In the EU *Campylobacter* burden was estimated at 8.28 DALY per 100,000 population [76], while in Australia estimates were 81.6 DALY per 100,000 population [77].

Outbreaks

Outbreaks of *Campylobacter* spp. gastroenteritis in high-income settings are reported less frequently than the incidence of infection might otherwise suggest. Reviews of outbreaks in

these settings reveal that poultry meat, particularly undercooked or raw chicken, is often identified as a food vehicle or putative source of cross-contamination, although the relative importance of this exposure varies between settings [56, 78, 79]. Poultry-liver containing foods, such as pâté, have become particularly well-recognised as transmission vehicles during foodborne outbreaks [80, 81]. Another significant outbreak risk is the ingestion of unpasteurised or raw milk [56]. Ground and surface water contamination are also important causes of often large-scale events [82, 83] but the frequency of waterborne outbreaks varies considerably between countries. Other less frequently reported outbreaks sources include direct zoonotic transfer from animals [84], environmental exposure [85] and person-to-person transmission, including via sexual contact [86].

This chapter has provided an overview of key microbiological, epidemiological and clinical considerations with regards to campylobacteriosis, with a deliberate focus on comparisons involving high-income settings. In the following chapters key facets of *Campylobacter*'s epidemiology in Australia will be examined using the three key themes of incidence, outbreaks and outcomes, with the latter focused on hospitalisation. Each of the thematic chapters is based around one or more studies, presented as published peer review manuscripts. A background to each of themes and studies will also be provided, in addition to details on study rationale and methodologies beyond what has been described in the accompanying manuscripts. A final discussion chapter will review the findings from the thematic analyses chapters, with the intention of assessing the clinical and public health significance of *Campylobacter* infection in Australia.

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Chapter 2 – Examining the incidence of infection with *Campylobacter* spp. in Australia



Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Manuscript 1

Title: The campylobacteriosis conundrum—examining the incidence of infection with *Campylobacter* sp. in Australia, 1998–2013

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CAMERON MOFFATT

Candidate – Print Name

MD Kirk

Signature

17/12/20

Date

Endorsed

Professor Martyn Kirk

Primary Supervisor – Print Name

MD Kirk

Signature

29/12/2020

Date

Cathy Banwell

Delegated Authority – Print Name

Cathy Banwell

Signature

3/01/2021

Date

In this chapter I examine the use of routinely collected surveillance data to describe the incidence of campylobacteriosis in Australia between 1998 and 2013. Surveillance data are especially valuable for assessing the health status of a population, providing the scientific and factual detail essential for informed decision-making around prevention and control efforts [1]. An important use of surveillance data is to measure disease occurrence in a population via rates, with incidence referring to the number of new illnesses diagnosed during a given period in a specified population [2]. Use of measures such as incidence rates as well as more advanced rate comparisons over time are important in aiding the development and evaluation of future disease impact, prevention, and control strategies [3]. In Australia, surveillance for campylobacteriosis utilises a passive, laboratory-based approach, with reporting of cases mandated under individual state and territory public health legislation [4, 5]. For the purposes of national surveillance, de-identified notification data are forwarded by states and territories to the Australian Government Department of Health [4].

As described in Chapter 1, *Campylobacter* is the leading cause of bacterial gastroenteritis in Australia and other comparable high-income settings, with the incidence of infection observed to be increasing [6]. In addition to high crude rates of campylobacteriosis reported in Australia [5], burden of disease estimates project in excess of 230,000 infections per annum, including 3,000 associated hospitalisations [7], 12,500 ReA cases and 70 GBS cases [8]. Trend analyses conducted in high-income settings have also provided evidence suggesting changes in the age structure for *Campylobacter* infections, with increasing rate of incidence predicted among older age-groupings [9]. *Campylobacter*'s unique epidemiological features, including gender disparity, age distribution and seasonality [6] are also amenable to review using incidence based methods. Despite the impact of campylobacteriosis in Australia, there was an identified need for a detailed examination of disease incidence [5]. Consequently this analysis of surveillance data, including modelling of incidence trends,

represents an important contribution to understanding the epidemiology of campylobacteriosis in Australia.

The study aims are described in detail in the manuscript accompanying this chapter but in summary I seek to describe the incidence of campylobacteriosis over time, looking in particular at trends by age group, gender and locality, with the latter studied at the level of Australian states and territories. Seasonality was included as a secondary aim. A description of the negative binomial regression model used is also provided in the manuscript's methods section but it is appropriate that I provide some background to this approach, including a practical rationale for its use. Surveillance data, including those used in this analysis, most often take the form of discrete count data, a data type where observations for dependent variables have non-negative integer values [10]. In modelling such data it is important to understand what probability distribution will be most appropriate, with the conventional distribution used in predicting the probability of events occurring over time being the Poisson distribution [10]. Application of a Poisson distribution to surveillance data however is problematic. In reality the distribution of *Campylobacter* notifications will vary considerably when assessed against independent variables of interest such as age, gender, location or season. This results in overdispersion of the data, a feature characterised by the sample variance exceeding the mean, a violation of a key assumption of Poisson distribution [11]. In other words, risk of campylobacteriosis among the general population is not constant, with this being evidenced by characteristics such as higher crude rates of illness in the very young and among males [6]. As an alternative, negative binomial distribution can be used to account for the underlying error (bias) structure in surveillance data, using an additional input parameter to adjust the variance independently from the mean [11]. Use of negative binomial regression has become well established in the analysis of surveillance data for a variety of enteric pathogens including salmonellosis [12] and giardiasis [13]. In Stata™, the negative

binomial regression command also includes results for a Poisson model, enabling direct comparison of both distributions upon the data. A dispersion statistic, the likelihood ratio (LR) chi square test is included with this output. For the accompanying manuscript this revealed a very large dispersion parameter $\alpha = 0$ (LR 4739.91, $p < 0.0001$), justifying the use of a negative binomial approach. Limitations to this study have been addressed in the accompanying manuscript but some important considerations for future examination of incidence would include the impact of culture independent testing on incidence rates [14, 15] and examination of incidence using different location identifiers, for example comparing urban versus rural rates of infection [16, 17].

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The campylobacteriosis conundrum – examining the incidence of infection with *Campylobacter* sp. in Australia, 1998–2013

C. R. M. MOFFATT¹*, K. GLASS¹, R. STAFFORD², C. D'ESTE¹ AND M. D. KIRK¹

¹ National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, Australia

² OzFoodNet, Communicable Diseases Branch, Queensland Health, Brisbane, Australia

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SUMMARY

Campylobacter sp. are a globally significant cause of gastroenteritis. Although rates of infection in Australia are among the highest in the industrialized world, studies describing campylobacteriosis incidence in Australia are lacking. Using national disease notification data between 1998 and 2013 we examined *Campylobacter* infections by gender, age group, season and state and territory. Negative binomial regression was used to estimate incidence rate ratios (IRRs), including trends by age group over time, with post-estimation commands used to obtain adjusted incidence rates. The incidence rate for males was significantly higher than for females [IRR 1·20, 95% confidence interval (CI) 1·18–1·21], while a distinct seasonality was demonstrated with higher rates in both spring (IRR 1·18, 95% CI 1·16–1·20) and summer (IRR 1·17, 95% CI 1·16–1·19). Examination of trends in age-specific incidence over time showed declines in incidence in those aged <40 years combined with contemporaneous increases in older age groups, notably those aged 70–79 years (IRR 1998–2013: 1·75, 95% CI 1·63–1·88). While crude rates continue to be highest in children, our findings suggest the age structure for campylobacteriosis in Australia is changing, carrying significant public health implications for older Australians.

Key words: *Campylobacter*, epidemiology, foodborne infections, foodborne zoonoses, incidence.

INTRODUCTION

Campylobacter sp. are internationally significant pathogens, causing an estimated 96 million cases of foodborne illness annually [1]. Campylobacteriosis presents as an acute self-limiting enteritis, characterized by watery diarrhoea, abdominal pain and fever, with symptoms lasting for about 1 week [2]. In addition, *Campylobacter* infections can result in a number of

extra-intestinal manifestations that include bacteraemia, Guillain-Barré syndrome and reactive arthritis [3].

Despite campylobacteriosis being one of the most common causes of foodborne illness in industrialized countries, outbreaks of disease are less frequently reported, with most cases thought to be sporadic, in that they are otherwise unrelated to each other [4]. Poultry are recognized as a major reservoir for *Campylobacter* sp., leading to contamination along the production chain and transmission to humans through contaminated meat at the retail level [5]. Other domesticated animals including cattle and pigs, and environmental sources such as contaminated water, also play a role in the transmission of infection to humans [3].

* Author for correspondence: Mr C. R. M. Moffatt, National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, Australia, 2602.
(Email: cameron.moffatt@anu.edu.au)

In Australia, the crude incidence of *Campylobacter* infections was 115.8 cases/100 000 population or 17 733 notifications in 2011 [6]. As such, Australia has one of the highest rates of infection in the developed world; being ten times that of the United States, double that seen in the European Union, but about 25% less than in New Zealand [5]. International data also suggests changes in the age structure of campylobacteriosis, with increasing and decreasing rates of incidence reported across different age strata in England and the United States [7, 8].

Notifications, however, represent only a small proportion of all cases, with an estimate of underreporting in Australia showing that for every 100 notifications, 1001 (95% credible interval 664–2251) cases of campylobacteriosis occur in the community [9]. Further Australian estimates have suggested that 234 000 domestically acquired infections occur each year, including 3200 hospital admissions [10]. Despite the high incidence of campylobacteriosis, there have been no published studies describing the epidemiological patterns and national disease trends in Australia. To improve the understanding of the reported incidence of campylobacteriosis in Australia we compared the rates of infection by sex, age group, season, and Australian states and territories, including trends over time across age groups.

METHODS

In this study, we used national data on reported cases of campylobacteriosis in Australia to analyse disease incidence by gender, age group, season and state and territory from 1998 to 2013. Campylobacteriosis is a notifiable condition in all Australian states and territories, except New South Wales (NSW), with all states and territories, except NSW, having public health legislation mandating its reporting by doctors and/or pathology providers [11]. A confirmed case requires laboratory definitive evidence of the isolation or detection of *Campylobacter* sp. [12]. Since 1991, the states of Queensland, South Australia (SA), Tasmania, Victoria, and Western Australia (WA); and the two territories: the Australian Capital Territory (ACT) and the Northern Territory (NT) have all collected and reported core data on cases to the National Notifiable Diseases Surveillance System (NNDSS). Ethics approval for this study was granted by the Australian National University Human Research Ethics Committee.

Data sources

We requested de-identified campylobacteriosis NNDSS notifications (including 'notification receive date', 'true onset date', 'diagnosis date', 'age at onset', and 'sex') for each state and territory for 1991–2014 from the Communicable Disease Network of Australia (CDNA). Because of incompleteness of some NNDSS data fields we restricted our analysis to cases with diagnosis dates from 1998 to 2013 inclusive. We also removed 2014 data from our final analysis because of significant changes in diagnostic practices in Australian primary testing laboratories, namely the widespread introduction of culture-independent diagnostic methods. 'Diagnosis date' was used for all analyses, which is defined as illness onset date, or where onset date is unknown, the earliest of the specimen collection date, the notification date, or the date the notification is received. Detail on species and postcode locations for notifications was not requested.

Rates of illness/100 000 population were calculated using the mid-year (June quarter) estimated resident population by age and sex for each state and territory, for each year between 1998 and 2013 from the Australian Bureau of Statistics (ABS) [13, 14].

Analysis

The primary aim of our analysis was to examine the reported incidence of campylobacteriosis over time, across age groups and between states and territories. Age was categorized into the following groups for descriptive analysis <1 year, 1–4 years, 5–9 years and in 10-year age groups from 10–19 years until ≥80 years. We defined seasons as summer (December, January, February), autumn (March, April, May), winter (June, July, August) and spring (September, October, November). ABS population numbers, obtained as the mid-year (30 June estimate) by age, sex and state and territory for each year, were used as denominators in the calculation of population incidence rates. Initial descriptive analysis included calculation of crude incidence rates/100 000 population by age group, sex, and state. Mean age of males and females was compared by *t* test. We then used negative binomial regression to estimate incidence rate ratios (IRR) with 95% confidence intervals (CIs) by sex, season, state, and trend over time by age group. *P* values from the *Z* statistic for the null hypothesis that the coefficient was zero are also

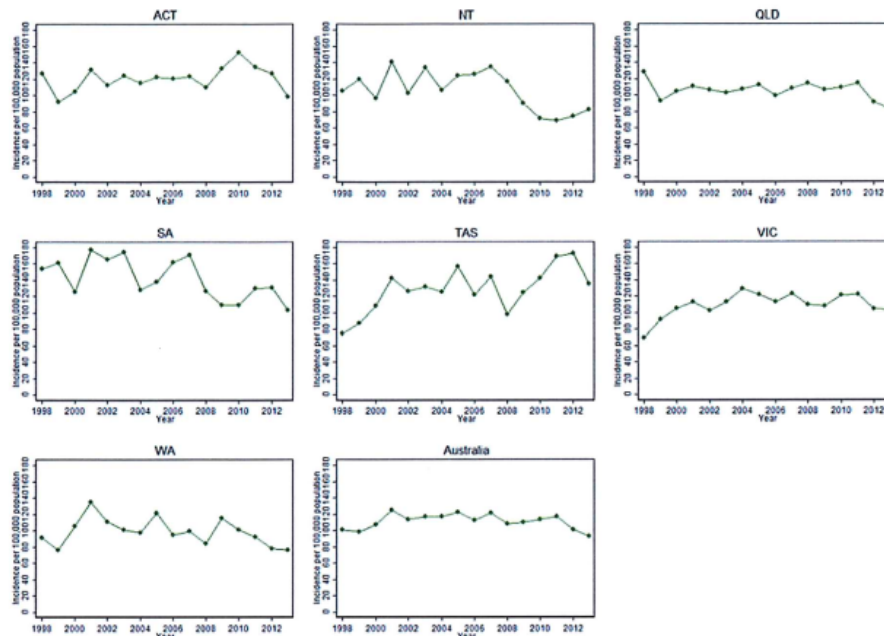


Fig. 1. Crude incidence rates for campylobacteriosis for Australia and individual states and territories, 1998–2013.

presented. We assumed a linear time trend for incidence rates, using the interaction between age group and year to produce a trend over time, with year defined as the year of diagnosis and treated as a continuous variable. We also used post-estimation commands to estimate incidence rates for sex, state and year and total changes in incidence from 1998 to 2013 by age group. For the final model, 10-year age groups from 0–9 years until ≥ 80 years were used as a reduced number of age groups yielded a better model based on both Akaike's Information Criterion and Bayesian Information Criterion. All statistical analyses were performed using Stata v.14 (StataCorp, USA).

RESULTS

Descriptive analysis

There were 246 151 notifications to NNDSS of campylobacteriosis with diagnosis dates between 1 January 1998 and 31 December 2013. Complete data was obtained on the state or territory of residence

of all these cases. Age at onset data was missing for 451 (0.18%) cases, with data on gender missing for 605 (0.25%) cases. There were 72 (0.03%) cases where both age at onset and gender data were missing. In total, 1128 (0.46%) cases were excluded from the final dataset, giving a total of 245 023 campylobacteriosis cases for inclusion in the analysis. The male:female ratio was 1.2:1, with males comprising 133 187 (54.4%) of cases. The mean age at onset for campylobacteriosis was 33.9 years (s.d. = 23.28, minimum <1, maximum 105 years). For females, the mean age was 35.1 years (s.d. = 23.31, minimum <1, maximum 105 years), and for males it was 32.9 years (s.d. = 23.20, minimum <1, maximum 105 years) (t test 24.3, $P < 0.001$).

Crude incidence rates for campylobacteriosis in Australia and for individual states and territories are shown in Figure 1. Nationally, crude incidence varied over time, with the highest annual rate seen in 2001 (124.7/100 000), decreasing to 92.8/100 000 in 2013. There was no obvious increasing or decreasing trend over time during that period. For states and territories crude incidence also varied over the period of

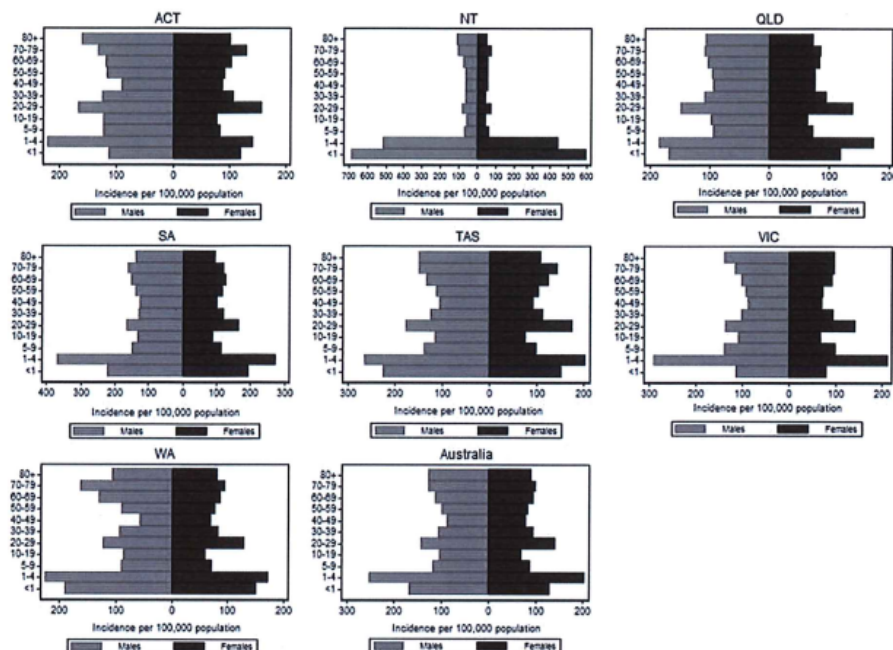


Fig. 2. Crude incidence rate pyramids by gender and age group for Australia and individual states and territories, 1998–2013.

reporting, being as high as 177.5/100 000 in SA in 2001 and 172.2/100 000 in Tasmania in 2012, to as low as 69.2/100 000 in Victoria in 1998 and 66.7/100 000 in the NT in 2011.

Nationally the highest crude age-specific rates were observed in children aged between 1 and 4 years, with 254.5 cases/100 000 population in males and 204.2 cases/100 000 in females, with the lowest rates observed in females aged 10–19 years (69.7 cases/100 000 population). Males had consistently higher rates of infection across all age groups. Crude sex and age-specific patterns of incidence were similar across most states and territories (Fig. 2). However, rates for NT children, in particular those aged <5 years, were markedly higher than elsewhere in Australia, reaching 684.7 cases/100 000 and 599.3 cases/100 000 for males and females aged <1 year and 515.1/100 000 and 445.7/100 000 for males and females aged 1–4 years, although these rates were determined on the basis of smaller case numbers in these sex and age strata than in other states and territories.

Factors associated with incidence

The rate of infection in males was 20% higher compared to females (Table 1: IRR 1.20, 95% CI 1.18–1.21). Nationally, notifications were shown to have a distinct seasonality, with similar rates in winter as autumn and statistically significant higher rates in both spring (IRR 1.18, 95% CI 1.16–1.20) and summer (IRR 1.17, 95% CI 1.16–1.19). Compared to the state of Victoria (the reference category), the highest IRR for *Campylobacter* infection was observed in the NT (IRR 1.40, 95% CI 1.34–1.45), with significantly higher IRRs also observed in ACT, SA and Tasmania. Significantly lower IRRs for *Campylobacter* infection were observed in both Queensland (IRR 0.96, 95% CI 0.95–0.98) and WA (IRR 0.91, 95% CI 0.89–0.93).

Trends over time

Examination of the interaction between age group and year showed significant differences in the trends over

Table 1. Negative binomial regression for *Campylobacter* notifications by gender, season, state and age group and time, Australia 1998–2013

	Notifications (<i>n</i> = 245023)	IRR	95% CI	<i>P</i> value
Gender	(Reference: female, <i>n</i> = 111 836)			
Male	133 187	1.20	1.18–1.21	<0.001
Season	(Reference: autumn, <i>n</i> = 55 972)			
Winter	56 518	1.01	0.99–1.03	0.26
Spring	66 135	1.18	1.16–1.20	<0.001
Summer	66 398	1.17	1.16–1.19	<0.001
State	(Reference: Victoria, <i>n</i> = 89 369)			
Australian Capital Territory	6581	1.31	1.27–1.35	<0.001
Northern Territory	3576	1.40	1.34–1.45	<0.001
Queensland	67 193	0.963	0.948–0.978	<0.001
South Australia	35 234	1.31	1.29–1.33	<0.001
Tasmania	10 145	1.31	1.28–1.35	<0.001
Western Australia	32 925	0.910	0.894–0.926	<0.001
Total change in incidence by age group, 1998–2013				
0–9 years	46 944	0.63	0.60–0.66	<0.001
10–19	26 160	0.97	0.92–1.03	0.35
20–29	45 195	0.78	0.74–0.81	<0.001
30–39	32 972	0.89	0.84–0.94	<0.001
40–49	27 639	1.06	1.01–1.12	0.03
50–59	24 954	1.13	1.07–1.20	<0.001
60–69	19 609	1.36	1.28–1.45	<0.001
70–79	13 896	1.75	1.63–1.88	<0.001
≥80	7654	1.72	1.57–1.89	<0.001

IRR, Incidence rate ratio; CI, confidence interval.

time in different age groups (Table 1, Supplementary Fig. S1). Adjusted rates of incidence between 1998 and 2013 decreased for younger age groups (i.e. those aged <40 years), while for older age groups there were increases in incidence of campylobacteriosis (Fig. 3). Significant declines over the 15-year study period were observed in children aged 0–9 years (IRR 0.63, 95% CI 0.60–0.66). The largest increases over time were observed in older age groups, notably the 70–79 years (IRR 1.75, 95% CI 1.63–1.88) and ≥80 years (IRR 1.72, 95% CI 1.57–1.89) age groups.

DISCUSSION

Considerable variations in the crude incidence of campylobacteriosis among Australian states and territories and between age groups over time were observed. While crude rates of disease remain highest in the very young, our findings support a shift in the age structure of campylobacteriosis in Australia, with IRRs increasing for older age groups over time. Further examination of predicted age-specific rates indicates a declining incidence in cases aged <40 years but combined with a concomitant rise in

incidence in older age groupings, notably those aged 70–79 years. Our analysis also affirms male gender to be significantly associated with a higher incidence of infection, along with the occurrence of a distinct seasonality with incidence rising markedly over the Australian spring and summer.

It has been suggested that over the past decade there has been an increase in campylobacteriosis in higher-income countries [3]; however, examination of published incidence rates shows there are considerable inter-country variations in incidence as well as between regions within individual countries [15]. Increases in overall incidence have been observed in the European Union [16], the United States [17] and the UK [7] but Japan has reported no discernible change [18], while in New Zealand, long recognized as having highest rates of campylobacteriosis, marked declines in incidence have been observed following interventions in poultry primary production and processing [19]. In Australia, national incidence has remained high but with the direction of any national trend being more difficult to discern, in part because of the 'regional' variations between states and territories. Due to the size of the Australian continent there is

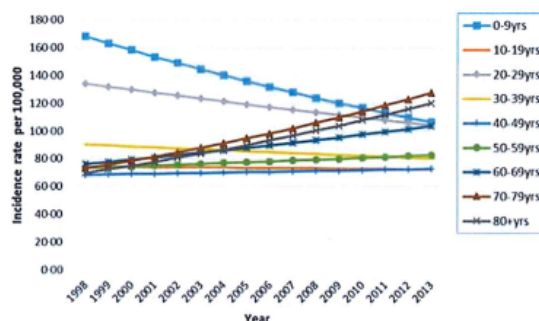


Fig. 3. Negative binomial regression margin plot for predicted incidence of campylobacteriosis by age group in Australia.

considerable climatic diversity. This ranges from tropical and monsoonal zones in the north, subtropical and temperate zones along the more populous eastern seaboard, smaller Mediterranean zones in the south and southwest, and a dominant semi-arid and desert zone covering the sparsely populated interior [20]. Given the seasonal patterns and climatic sensitivities of *Campylobacter* sp. [21] our findings of variations in incidence across regions of Australia are not wholly unexpected. Other explanations for the increases and decreases in both unadjusted and adjusted incidence over time might include differences in population exposures and behaviours, differences in laboratory detection and surveillance methods, differences in primary production practices and their regulation, or differences in relative contributions of assorted *Campylobacter* reservoirs to human disease [3].

Our findings from analysis of crude rates are broadly consistent with a number of studies from other high income countries that report a bimodal age-related pattern of incidence, with the highest infection rates in children aged <5 years, and with a second peak seen in younger adults aged between 20 and 29 years [22, 23]. These findings may be a reflection of differences in the relative contribution of environmental factors involved in the causal pathway of campylobacteriosis across these different age groups [24]. For example the high incidence shown for young children could reflect their more active exploration of their environment using hand-to-mouth behaviour [25], with the high incidence seen in NT children perhaps indicative of climatic differences or some other undefined environmental risks. In other age groups, poor hygiene practices as well as increased risky eating behaviour subsequent to moving out of

the family home have been tendered as explainers for the peaks seen in young adults [26, 27]. A further consideration is the impact of acquired immunity on the epidemiology of campylobacteriosis [27].

While acknowledging a 'general' bi-modal pattern of age-related incidence for campylobacteriosis, we would also contend that in the Australian context our crude and adjusted incidence patterns actually demonstrate a tri-modal pattern, with a third incidence peak seen in those aged >60 years. Adults aged >65 years are recognized as being more susceptible than younger adults to certain enteric infections, including campylobacteriosis. A number of age-related factors may also contribute to their increased susceptibility and disease severity, including weakening of the immune system, changes to the gastrointestinal tract, a higher prevalence of comorbid conditions and more frequent use of antacids and immunosuppressant medication [28].

Our finding of a predicted increase in incidence over time among older adults is supported by analyses of data from England and Wales suggesting the age structure of campylobacteriosis has shifted, with older persons emerging as the population most at risk [7, 29]. In addition to the host factors previously described, social factors such as population ageing and demographic changes, including post-war population increases and the 'baby boom' of the 1960s may also play a role [29]. Given that the proportion of the Australian population aged >65 years is projected to increase from 14% (3.2 million) in 2012 to around 19% (5.8 million) in 2031 [30] any such change in the age structure of disease could carry significant health system implications. Studies of older persons infected with *Campylobacter* sp. show increased

hospitalization and mortality, with clinical care further complicated by higher levels of comorbidities and risk for invasive infection [8, 31]. However, whether such a shift in the age structure of campylobacteriosis across high-income countries can be generalized is less certain, with a recent US study showing a decreasing rate of campylobacteriosis with increasing age [8].

That male gender was significantly associated with increased risk for infection in our study is a finding consistent with the epidemiology of *Campylobacter* in high-income country settings. This was further reflected in males having consistently higher rates of infection across all age groups, with the exception of those aged between 20 and 29 years [23, 32]. Explanations for the predilection towards males are not easily reconciled. Given the large differences in incidence between males and females in the youngest age groups where behavioural differences might be less pronounced, physiological differences may play a role in higher male disease incidence. This hypothesis is supported by an animal model showing both infection and shedding rates for *C. jejuni* to be greater in male mice [33].

Campylobacteriosis has been shown to exhibit a distinct seasonality in temperate regions, although clear reasons for this feature have proven difficult to ascertain [25]. Our finding, demonstrating a sharp rise in IRR in spring, with continuing and significantly elevated rates in summer is consistent with previous comparisons of high income countries in both the Northern and the Southern Hemispheres [21]. The consistency of a bacterial infection to exhibit summer peaks suggests the direct effect of a large scale environmental influence on a shared exposure route [34]. Although we did not examine any interaction between temperature and incidence, it is nevertheless plausible that increasing spring temperatures and the maintenance of high temperatures over summer greatly increase the risk for foodborne transmission of *Campylobacter* [35].

Poultry meat has been demonstrated to be the predominant foodborne source of campylobacteriosis in developed countries [3, 5], with such findings arguably applicable to the Australian context, despite a current paucity of local source attribution data. In Australia, the poultry meat sector is particularly large and is dominated by two main producers, with primary processing occurring in all states [36]. In 2012, Australia introduced a national Primary Production and Processing Standard for poultry meat [37] but there

is little publicly available data on what, if any, industry-initiated actions occurred between 1998 and 2013. Access to such information could have been used to model the effects of interventions on incidence. Given the increasing recognition that a 'One Health' approach, including greater cooperation and engagement by stakeholders is necessary to reduce the national burden of campylobacteriosis [38] we draw particular attention to the importance of data sharing between animal industries, agriculture and human health agencies to gain better understanding of campylobacteriosis in Australia. Australian stakeholders (e.g. veterinarians, scientists, policy makers, public health authorities, and industry) may benefit from undertaking closer examination of international successes, particularly in New Zealand, where integrated surveillance strategies have improved the understanding of disease drivers and contributed to a significant decline in disease incidence [39].

Limitations

There are a number of limitations to this study. Because campylobacteriosis is recognized as a largely sporadic infection, minimal public health data is collected for most cases and we were unable to exclude overseas acquired and outbreak associated cases from our analysis. Despite overseas travel previously being identified as a risk factor for infection in Australia, absolute numbers of cases with this risk have previously been reported as being small [40], leading us to conclude that most infections are likely to be domestically acquired. Similarly the impact of outbreaks on campylobacteriosis numbers is likely to be negligible given recognition that outbreaks are infrequent events relative to overall incidence [4]. Another potential limitation was an absence of comprehensive speciation data. We assumed that most infections were caused by *C. jejuni* and to a lesser extent *C. coli*. There are however indications that *C. coli* might contribute a larger number of infections than previously thought [41], with the importance of other emerging pathogenic species largely unknown in Australia. Similarly our dataset lacked geographic precision beyond the level of state or territory. Australia is a large and geo-climatically diverse continent and significant differences between urban and rural incidence have been demonstrated elsewhere internationally [15]. Such detail would be useful in further exploring differences in age, gender and origin of infection. Finally the increasing use by primary testing

laboratories of culture-independent testing, notably nucleic acid tests, to diagnose enteric infections carries implications for disease surveillance and reporting with incidence rates likely to increase due to improved sensitivity in detection [42]. This latter point directly influenced our decision to exclude 2014 notifications from the analysis because of the widespread uptake of these methods across Australia in that year.

CONCLUSIONS

Our examination of the incidence of campylobacteriosis in Australia provides further illustration of the epidemiological complexities surrounding this common enteric pathogen. Australia continues to have a high rate of infection but considerable variation in incidence exists between sexes, age groups, and states and territories. While common or similar sources of transmission might be responsible for most disease across the different age groups, a transition to higher rates of disease in older persons carries significant implications for public health and clinical care. As such there is a need for improved understanding of risk factors specific to older Australians, combined with targeted public health messaging to educate this group of increased disease risk.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <https://doi.org/10.1017/S0950268816002909>.

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DECLARATION OF INTEREST

None.

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Chapter 3 – Outbreaks of campylobacteriosis infection in Australia



Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Manuscript 2

Title: Characteristics of *Campylobacter* Gastroenteritis Outbreaks in Australia, 2001 to 2016.

Authors: Moffatt CR, Fearnley E, Bell R, Wright R, Gregory J, Sloan-Gardner T, Kirk M, Stafford R.

Publication outlet: Foodborne Pathogens and Disease. 2020 May 1; 17(5):308-15

Current status of paper: Published

Contribution to paper: The candidate conceived the study design, undertook data analysis and drafting of the manuscript.

Senior author or collaborating authors endorsement: MD Kirk

Manuscript 3

Title: A large outbreak of *Campylobacter jejuni* infection in a university college caused by chicken liver pâté, Australia, 2013.

Authors: Moffatt CR, Greig A, Valcanis M, Gao W, Seemann T, Howden BP, Kirk MD.

Publication outlet: Epidemiology & Infection. 2016 Oct; 144(14):2971-8.

Current status of paper: Published

Contribution to paper: The candidate managed the outbreak investigation, performed the epidemiological analysis and drafted the manuscript.

Senior author or collaborating authors endorsement: MD Kirk

<u>CAMERON MOFFATT</u>	<u>[Signature]</u>	<u>17/12/20</u>
Candidate – Print Name	Signature	Date

Endorsed

<u>Professor Martyn Kirk</u>	<u>MD Kirk</u>	<u>29/12/2020</u>
Primary Supervisor – Print Name	Signature	Date
<u>C. Banwell</u>	<u>Cathy Banwell</u>	<u>3/1/21</u>
Delegated Authority – Print Name	Signature	Date

In this chapter I examine the theme of outbreaks of campylobacteriosis, with the chapter centred on two published manuscripts. The first manuscript provides a review of national summary data on outbreaks of campylobacteriosis identified in Australia between 2001 and 2016. The second manuscript describes the detailed findings from a public health investigation into an individual outbreak linked to consumption of poultry-liver pâté, including use of genomic data to support the interpretation of findings.

In infectious disease epidemiology an outbreak is most usually defined in terms of a sudden increase in disease frequency, related to time, place, and within a defined population [1]. In Australia, foodborne outbreaks are defined as incidents where ≥ 2 persons experience a similar illness after consuming a common food or meal, and where through use of combinations of descriptive and analytical epidemiological evidence, food and traceback microbiology and food safety investigation, a food or meal is implicated as the cause [2]. As shown in Table 1 of the first manuscript accompanying this Chapter, this definition can be readily adapted for specific pathogens like *Campylobacter* spp. and for transmission routes other than food.

Undertaking surveillance and review of foodborne and enteric disease outbreaks serves a number of important purposes, including the identification of common and high risk food vehicles, the identification of new and emerging pathogens, the identification of settings where outbreak-associated foods are prepared and eaten, the identification of actionable points where contamination can be reduced and the description of trends in outbreaks over time [3]. In Australia, surveillance for outbreaks of foodborne and enteric disease is conducted via the OzFoodNet Network, a group established to improve national surveillance and conduct applied research into the causes of foodborne illness [4]. OzFoodNet maintains a National Outbreak Register, with all states and territories contributing standardised outbreak summary data to this system [4].

As described in the preceding chapters, a noted feature of the epidemiology of *Campylobacter* infections in high-income settings has been the infrequency of outbreak events and associated cases, relative to the numbers of disease notifications and the incidence of disease [5, 6]. However this feature is perhaps not as easily generalised, with outbreak surveillance data from countries including Germany and the US suggesting that *Campylobacter* outbreaks can occur with greater frequency [7, 8]. By comparison, an earlier Australian review of *Campylobacter* outbreaks occurring between 2001 and 2005, found them to be relatively uncommon events, with <1% of laboratory confirmed infections being linked to known outbreaks [9]. Since that time further reporting in Australia has suggested an increase in outbreak occurrence, with the emergence of poultry-liver containing foods viewed as being important transmission vehicles [10]. Outbreaks caused by direct zoonotic transmission have also been reported, highlighting the potential for non-foodborne transmission routes [11]. More recently greater consideration has also been given to the potential impact of genomics on outbreak surveillance and investigation, with WGS being advocated as a means of improving outbreak detection among seemingly sporadic cases of infection [12].

Given campylobacteriosis is responsible for a large and growing burden of disease within Australia and other high-income countries, and with the availability of additional outbreak data from 2007 to 2016, it was appropriate to undertake a detailed re-examination of outbreaks and their impact in Australia. The research aim for the first manuscript accompanying this chapter was to provide a contemporary understanding of documented *Campylobacter* outbreaks in Australia. Both descriptive epidemiology and statistics were used, with a particular emphasis placed on reviewing transmission routes and the evidence used in determining modes of infection. Drawing upon previous experience in the development of strength of evidence indicators for outbreak data derived from the National

Outbreak Register was beneficial to this process [13, 14]. While the burden of campylobacteriosis is thought to be poorly estimated by source attribution when using outbreak data due to the infrequency of events [15], descriptive reviews of outbreaks data can still provide useful insight into potential reservoirs, risk factors and investigative issues associated with this common pathogen.

The second manuscript included under the outbreak theme describes an investigation following an outbreak of *C. jejuni* gastroenteritis among attendees at a university college dinner. Given the outbreak setting and apparent infrequency of *Campylobacter* outbreaks, this was viewed as a valuable opportunity for public health learning, with a retrospective cohort study being commenced as part of the investigation. This form of observational study is regarded as the method of choice for the investigation of acute foodborne outbreaks in a well-defined population [16]. The primary hypothesis tested was that a menu item served at the dinner was responsible for causing illness among guests. A further analysis feature of this study was the use of logistic regression to control for potential confounding. Logistic regression is statistical modelling technique that is applied to estimate the simultaneous effect of a set of covariates (i.e. predictor or independent variables) on the risk of a binary outcome [17], in this instance either developing (or not developing) gastroenteritis following attendance at the dinner. Binary outcomes in cohort studies are commonly analysed via logistic regression to obtain odds ratios. In this instance, a suggestion by a reviewer to use a general linear model was adopted for the second manuscript, enabling the effect estimate to be reported as a relative risk (RR). This also maintained uniformity of reporting outcomes between the univariate and multivariate results, as logistic regression reports an odds ratio. From a practical perspective however, the direction of the effect estimates did not differ between models, validating public health actions with regards to liver pâté being the implicated food vehicle. Use of logistic regression will be discussed in more detail in Chapter

4, where the confounding effects of clinical data, in particular comorbidity and ageing, have a greater impact on determining risk profiles.

While this thesis does not have a specific molecular epidemiological focus, it is important to provide some background to WGS as this was an important laboratory component of the investigation described in the second manuscript. Molecular methods, particularly Multi-Locus Sequence Typing (MLST) have been used extensively to subtype *Campylobacter* isolates. MLST lists nucleotide sequence variation among genes encoding proteins that are essential for metabolic function (so-called “housekeeping genes”), defining each isolate in terms of its sequence type (ST), which then can be grouped into clonal complexes (CCs) representing lineages presumably derived from a common ancestor [18]. While having been valuable in furthering understanding of the epidemiology of *Campylobacter* infections in humans and animals, MLST has limited ability to discriminate genetically related isolates within STs or determine differences in relationships within and between CCs [19]. More recently WGS methods have become increasingly available. These offer the benefit of comparative genomics, with the capacity to differentiate highly related strains and make inferences regarding the relationship between isolates [20]. This has important implications for food safety, including outbreak investigations, with WGS data being used by public health authorities to supplement epidemiological and traceback evidence [21].

It has been reported that regardless of the molecular approach used, the genomic diversity among epidemiologically linked isolates within an outbreak investigation will be limited to only a few changes [22]. However given previous experience from investigating a point source outbreak of campylobacteriosis in Australia [23], it was hypothesised that multiple strains could be found among epidemiologically linked isolates. This was subsequently demonstrated, with the implications addressed in the attached manuscript’s discussion section. A common measure of genetic relatedness obtained via WGS and now being used to

aid outbreak investigation are Single Nucleotide Polymorphisms (SNPs), or the number of nucleotide differences between isolates [21]. If there are a few SNP differences, the isolates might be considered as closely related, increasing the likelihood they came from the same source, while the presence of many (i.e. hundreds or thousands) SNP differences suggests the isolates are more distantly related, and unlikely to originate from the same reservoir population [21]. It is therefore important to place SNP distances into context using phylogenetic trees that show relationships between isolates. In the second manuscript both tree topology (Figure 2) and SNP distance (Table 2) are considered in the context of the epidemiological and environmental findings.

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Characteristics of *Campylobacter* Gastroenteritis Outbreaks in Australia, 2001 to 2016

Cameron R.M. Moffatt,¹ Emily Fearnley,^{1,2} Robert Bell,³ Rose Wright,⁴ Joy Gregory,⁵
Timothy Sloan-Gardner,⁶ Martyn Kirk,¹ and Russell Stafford³

Abstract

Campylobacter spp. are a globally important cause of bacterial gastroenteritis, with Australia experiencing higher rates of illness than many comparable high-income countries. Despite the high disease incidence, outbreaks of campylobacteriosis in Australia are infrequently detected and reported. We examined the epidemiology of *Campylobacter* outbreaks in Australia, with particular emphasis on assessing transmission routes and evidence as reported during public health investigations. A national register of enteric and foodborne disease outbreaks was used to summarize data on all *Campylobacter* outbreaks reported in Australia between 2001 and 2016. Outbreak data were reviewed and analyzed for trends over time. Additional information was sought from state and territory epidemiologists, to validate transmission routes. A total of 84 *Campylobacter* outbreaks were reported, with 51 (61%) being classified as foodborne. Specific food vehicles were identified for 33 (65%) outbreaks, with 28 (85%) implicating chicken or chicken-containing dishes. Although no increase in the proportion of foodborne *Campylobacter* outbreaks was observed, examination of specific food vehicles demonstrated a significant increase in outbreaks because of poultry-liver containing foods ($p=0.04$). One quarter of all 1042 outbreak-associated cases occurred in aged-care facilities (ACFs), including 17 associated hospitalizations and three deaths. After review of evidence data, 23 outbreaks (27%) were determined to have an unknown route of transmission, including 10 (43%) outbreaks occurring in ACFs. *Campylobacter* spp. remain a less commonly reported cause of gastroenteritis outbreaks in Australia. Although many reported outbreaks can be linked to foodborne transmission, over a quarter were unable to identify either a food vehicle or transmission source, particularly for outbreaks occurring in aged care. Increased efforts to improve evidence collection and understanding of transmission dynamics for outbreaks of campylobacteriosis, particularly in aged care, are required.

Keywords: *Campylobacter*, disease outbreaks, foodborne diseases, waterborne diseases, zoonoses, homes for the aged

Introduction

CAMPYLOBACTER spp. ARE an important cause of gastroenteritis and responsible for an annual global estimate of 96 million (95% UI 52–177 million) cases of foodborne infection (Kirk *et al.*, 2015). Although campylobacteriosis most commonly presents as a self-limiting enterocolitis, extraintestinal infections (e.g., bacteremia) and postinfectious complications

such as Guillain-Barre syndrome, reactive arthritis, and irritable bowel syndrome may also occur (Fitzgerald, 2015).

Poultry, particularly broilers, are recognized as the primary reservoir for foodborne infections, with ruminants such as cattle and sheep and monogastric species such as pigs also being important carriers (Kaakoush *et al.*, 2015). In addition to illness acquired through undercooked or cross-contaminated foods of animal origin, campylobacteriosis

¹National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, Australia.

²South Australian Department for Health and Wellbeing, OzFoodNet, Adelaide, Australia.

³OzFoodNet, Communicable Diseases Branch, Queensland Health, Brisbane, Australia.

⁴Australian Government Department of Health, OzFoodNet, Office of Health Protection, Canberra, Australia.

⁵Department of Health and Human Services, OzFoodNet, Communicable Disease Epidemiology and Surveillance, Melbourne, Australia.

⁶OzFoodNet, Communicable Disease Control, Health Protection Service, Australian Capital Territory Health Directorate, Canberra, Australia.

may also result from animal interactions, ingestion of unpasteurized milk, contaminated water, or less commonly through person-to-person contact (Kaakoush *et al.*, 2015).

In high-income settings like the European Union (EU) and England, where foodborne disease surveillance is well established, *Campylobacter* spp. are the most commonly reported enteric pathogens (European Food Safety Authority [EFSA], 2017; Nichols *et al.*, 2012). During 2016, 246,307 cases were reported among EU member states (notification rate 66.3 per 100,000 population) and 52,381 cases were reported in England and Wales (notification rate 89.7 per 100,000) (European Food Safety Authority [EFSA], 2017; Gastrointestinal Infections Department, 2018). Similarly in Australia, disease incidence remains high (Moffatt *et al.*, 2017a), with 24,239 confirmed cases reported in 2016, a national notification rate of 100.2 per 100,000 (Australian Government Department of Health, 2019).

Despite the high incidence and case numbers, *Campylobacter* outbreaks remain less frequently reported in Australia (Unicomb *et al.*, 2009; Moffatt *et al.*, 2017a). This contrasts markedly with *Salmonella enterica*, another enteric pathogen of public health significance, responsible for ~1000 outbreaks in Australia between 2001 and 2016 (Ford *et al.*, 2018). Nevertheless, outbreak data contribute to our understanding of *Campylobacter*'s epidemiology, showing food vehicles such as poultry-liver pâté have become an established cause of outbreaks internationally (Little *et al.*, 2010; Lanier *et al.*, 2018).

Using national outbreak and disease notifications data, we examined *Campylobacter* outbreaks in Australia, expanding

upon a previous assessment for the period 2001–2006 (Unicomb *et al.*, 2009). The aim of this study was to provide a contemporary understanding of the epidemiology of campylobacteriosis outbreaks in Australia, with particular focus on transmission routes and evidence levels obtained during investigations.

Materials and Methods

All Australian states and territories have public health legislation mandating the reporting of *Campylobacter* infections and suspected outbreaks of food or waterborne gastroenteritis (OzFoodNet Working Group, 2018). However, campylobacteriosis only became notifiable in the state of New South Wales (NSW) in 2017, falling outside of study parameters. OzFoodNet, a national network performing surveillance and investigation of enteric and foodborne disease in Australia, maintains a National Outbreak Register (hereafter called the Register) with all states and territories contributing outbreak data (Kirk *et al.*, 2008). Two states, NSW and Victoria, use local alternatives to the Register for recording details of nonfoodborne *Campylobacter* outbreaks.

Data were extracted from the Register providing details of *Campylobacter* outbreaks between 2001 and 2016. Information included nominated transmission routes, settings where outbreaks occurred, settings where food was prepared (if applicable), dates of outbreak notifications, implicated *Campylobacter* species (if known), numbers of persons exposed, numbers of cases, hospitalizations and deaths, types of epidemiological investigation (case-control study, analytical

TABLE 1. DEFINITIONS FOR OUTBREAKS OF CAMPYLOBACTERIOSIS BY TRANSMISSION ROUTE

Outbreak transmission type	Definition
Foodborne outbreak	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after consuming a common food or meal, and where analytical epidemiology or food microbiology implicates the food or meal as the source of illness
Suspected foodborne outbreak	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after consuming a common food or meal, and where compelling descriptive evidence from an epidemiological investigation and/or food safety inspection implicates the food or meal as the source of illness
Waterborne outbreak	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after exposure to a common water source (either drinking or recreational) and where analytical epidemiology or water testing implicates water as the source of illness
Suspected waterborne outbreak	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after exposure to a common water source (either drinking or recreational) and where compelling descriptive evidence from an epidemiological and/or environmental investigation implicates water as the source of illness
Person to person outbreak	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after exposure to a person or group of persons known or suspected to be infectious, or an environment where an infected person has been known to have contaminated and where illness onset dates suggest ongoing transmission
Animal to person outbreak	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after animal exposure and compelling descriptive epidemiological or environmental evidence and/or laboratory evidence implicates the animal as the source of illness
Unknown	An event where ≥ 2 persons are diagnosed with laboratory-confirmed campylobacteriosis after some common exposure but where a mode of transmission is unable to be determined
Unknown (revised)	An event where ≥ 2 persons are diagnosed with laboratory-confirmed <i>Campylobacter</i> infection after a common exposure but where a recognized mode of transmission is unable to be determined via either outbreak register detail and/or local review by a state or territory epidemiologist

TABLE 2. CHARACTERISTICS OF *CAMPYLOBACTER* OUTBREAKS BY TRANSMISSION ROUTES, AUSTRALIA 2001 TO 2016

Transmission route	No. outbreaks (% by route)	No. cases (% lab-confirmed)	Median no. cases (min. to max.)	No. hospitalizations (% cases)	No. deaths
Foodborne	51 (60.7)	723 (30.7)	10 (2 to 63)	51 (7.1)	2
Waterborne	5 (6.0)	104 (30.8)	22 (7 to 46)	5 (4.8)	0
Animal to person	2 (2.4)	16 (37.5)	8 (6 to 10)	1 (6.3)	1
Person to person	3 (3.6)	16 (81.3)	4 (3 to 9)	3 (18.8)	0
Unknown	23 (27.4)	183 (48.1)	6 (3 to 9)	12 (6.6)	0
Total	84 (100)	1042 (34.6)	7 (2 to 63)	72 (6.9)	3

cohort study, or case series), and levels of evidence obtained. Outbreak definitions were adapted from the Register's Data Dictionary (Version 1.5, December 2017) to describe outbreaks occurring through specific transmission routes (Table 1). Nominated food vehicles were grouped under the following categories: poultry-liver dishes; chicken kebabs; other chicken/chicken-containing dishes; chicken unspecified; other food vehicle; other poultry-meat; unpasteurized milk; and unknown food vehicle. For this dataset the term poultry is used in reference to domestic fowls, with poultry-liver referring to either chicken or duck and poultry-meat used in reference to duck alone. Other chicken/chicken-containing dishes describe food vehicles where chicken has been identified as the ingredient suspected of being contaminated (e.g., pasta dishes or dumplings). To examine trends in foodborne *Campylobacter* outbreaks we obtained annual totals for foodborne outbreaks reported between 2001 and 2016. Annual campylobacteriosis notification rates per 100,000 population were obtained from the National Notifiable Diseases Surveillance System (Australian Government Department of Health, 2019) for comparison against annual outbreak counts.

To provide greater etiologic certainty, outbreaks with a single laboratory-confirmed *Campylobacter* case or where additional enteric pathogens were detected were excluded. Also excluded were *Campylobacter* clusters. A cluster was defined as an increase in infections that are epidemiologically related in time, place, or person where investigations were unable to implicate a common mode of transmission or source of infection responsible for that increase (OzFoodNet Working Group, 2018).

Outbreak details were forwarded to state and territory foodborne disease epidemiologists, including queries regarding missing or potentially erroneous data. Epidemiologists were also asked to review local records to identify other outbreaks not identified in the Register, with this approach identifying one additional outbreak. We obtained separate details for nonfoodborne *Campylobacter* outbreaks from NSW and Victoria as both use local databases to record nonfoodborne outbreaks.

Each outbreak was assigned an evidence level based on published indicators of evidentiary strength for foodborne disease outbreaks (Moffatt *et al.*, 2016b). Options for evidence included the following: descriptive epidemiological evidence (hereafter called descriptive); statistical; laboratory and descriptive; descriptive and trace-back; laboratory and statistical; laboratory and trace-back; statistical and trace-back; and trace-back. For nonfoodborne outbreaks, options

referencing trace-back were not considered. Evidence levels were not assigned for outbreaks where the transmission route was unknown. If our reassessment of transmission differed to the original data, we asked state and territory epidemiologists to examine local records to assist with validation. If no compelling detail was available, our reassessment was adopted.

Data describing *Campylobacter* isolation in food and environmental samples were assessed and included detection in the following: unopened epidemiologically implicated food; opened epidemiologically implicated food; food consumed without epidemiological implication; other microbiological evidence; isolation from premises and equipment; no identification in laboratory samples; or no samples taken. A descriptive assessment of factors contributing to pathogen contamination and survival was also undertaken but excluded growth factors because of data paucity and a reduced likelihood for *Campylobacter* spp. to proliferate on foods (Park, 2002). Contributing factors to contamination of food or water included ingestion of contaminated raw product intended to be cooked, cross-contamination from raw ingredients, food handler contamination, storage in contaminated environment, ingestion of contaminated raw product intended to be consumed raw, or unknown. Contributing factors related to survival included insufficient time/temperature during cooking or reheating, inadequate disinfection, inadequate acidification, inadequate thawing and cooking, other process failure, or unknown. Evidence levels for contributing factors included assumed or suspected, confirmed through observation during inspection, confirmed verbally during inspection, confirmed with measured evidence, or unknown.

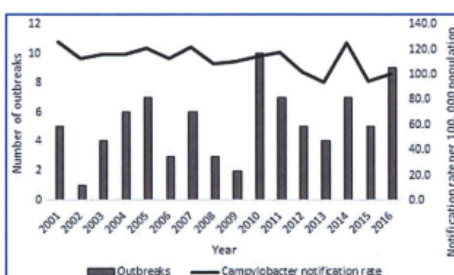


FIG. 1. Annual *Campylobacter* notification rates and outbreak counts, Australia, 2001–2016.

Data were analyzed using Microsoft Excel (Microsoft, 2013; Microsoft, Redmond, WA) and Stata SE version 13 (StataCorp, 2013; Stata Statistical Software: Release 13; StataCorp LP, College Station, TX). We used descriptive statistics, including chi-square tests for homogeneity and trend, to assess changes in the proportions of foodborne outbreaks reported over the study period. Examination of aged-care outbreaks used median tests to compare cases, hospitalizations, and outbreak duration between outbreaks classified with foodborne versus unknown transmission routes. The probability value for significance testing was ≤ 0.05 . Ethics approval was obtained from the Australian National University's Human Research Ethics Committee (Protocol: 2018/531).

Results

Between 2001 and 2016 we identified 84 *Campylobacter* outbreaks in Australia. Details on transmission route and associated disease burden are given in Table 2, with foodborne or suspected foodborne transmission (hereafter described as foodborne transmission or foodborne outbreaks) accounting for 61% (51/84) of outbreaks. Outbreaks were reported by all states and territories with the more populous states having higher outbreak counts (data not shown). Speciation detail was available for 44% (37/84) of outbreaks, with *Campylobacter jejuni* the dominant etiologic agent (35/37). Two outbreaks comprised mixed *Campylobacter coli* and *C. jejuni* infections. During this time annual notification rates for campylobacteriosis remained high, averaging >110 cases per 100,000 population. Conversely, the reported outbreak counts were small (median 5, min. 1 to max. 10), and varied between years (Fig. 1).

Characteristics of foodborne outbreaks by setting are given in Table 3. Among foodborne outbreaks, 39% (20/51) occurred in the setting of restaurants/cafes, followed by 16% (8/51) in ACFs, and 10% (5/51) in "other" settings, with the

latter including take-away food businesses (small-scale food venues providing made to order foods collected and eaten elsewhere by consumers). When compared with other transmission routes, associations with foodborne transmission were observed in restaurants ($\chi^2 = 16.99$ $p < 0.001$) and aged-care facilities (ACFs) ($\chi^2 = 7.41$ $p = 0.006$). Implicated foods were mostly prepared within the setting of the outbreak; however, five outbreaks involved foods prepared by commercial caterers, whereas molecular epidemiology linked another community outbreak to commercially produced chicken meat. Food vehicles were identified for 65% (33/51) of outbreaks, with poultry meat or offal implicated in 85% (28/33). Among these poultry-related food vehicles, liver dishes (e.g., pâté) comprised 39% (11/28), followed by other chicken-containing dishes (33%, 8/28), chicken kebabs (18%, 5/28), chicken unspecified (11%, 3/28), and duck (4%, 1/28). During the study period, OzFoodNet reported 2097 foodborne outbreaks (personal communication Rose Wright, February 13, 2019). After revising transmission route data, we determined that *Campylobacter* spp. accounted for 2.4% (51/2083) of foodborne outbreaks between 2001 and 2016. Although no significant trend in foodborne outbreaks caused by *Campylobacter* spp. was shown, we did observe a significant increase in the proportion of foodborne *Campylobacter* outbreaks linked to poultry-liver ($\chi^2 = 4.22$, $p = 0.04$). Among poultry-liver outbreaks, 73% (8/11) involved restaurants, 18% (2/11) involved commercial catering, whereas one outbreak involved pâté prepared in a private residence.

Nonfoodborne outbreak characteristics are given in Table 2. Before review, 11% (9/84) of *Campylobacter* outbreaks had an unknown transmission route. This increased to 27% (23/84) after we identified 14 outbreaks recorded as being foodborne but lacking the necessary evidence to meet the foodborne outbreaks definitions as given in Table 1. Among the most frequently identified settings for outbreaks with an unknown source were ACFs ($n = 10$), military facilities ($n = 4$), and private residences ($n = 4$). Among

TABLE 3. CHARACTERISTICS OF FOODBORNE *CAMPYLOBACTER* OUTBREAKS BY SETTING, AUSTRALIA 2001–2016

Outbreak setting	Foodborne outbreaks				
	No. outbreaks (all routes)	No. outbreaks (% foodborne)	No. cases (% lab-confirmed)	Median no. cases (min. to max.)	No. hospitalizations (No. deaths)
Restaurants	20	20 (100.0)	228 (28.9)	10 (2 to 35)	13
Aged care	22	8 (36.4)	143 (28.0)	14.5 (3 to 49)	10 (2)
Other settings ^a	5	5 (100.0)	85 (32.9)	5 (2 to 63)	1
Camps	7	3 (42.9)	43 (14.0)	14 (6 to 23)	0
Private residences	9	3 (33.3)	16 (50.0)	5 (4 to 7)	0
Schools	2	2 (100.0)	42 (38.1)	21 (6 to 36)	1
Other institutions	3	2 (66.7)	61 (14.8)	30.5 (5 to 56)	1
Picnics	2	2 (100.0)	8 (87.5)	4	0
Community	2	2 (100.0)	27 (100.0)	13.5 (3 to 24)	4
Military facility	5	1 (20.0)	19 (15.8)	19	19
Commercial caterer	1	1 (100.0)	11 (54.5)	11	1
Function	1	1 (100.0)	31 (12.9)	31	1
Workplace	1	1 (100.0)	9 (22.2)	9	0
Totals	81 ^b	51	723 (30.7)	10 (2 to 63)	51 (2)

^aIncludes three takeaway food establishments, a sporting club, and a dairy farm.

^bEighty-four outbreaks identified in total. Three nonfoodborne outbreaks occurred in settings not described above, that is, a child care center, a hospital, and an unknown setting.

TABLE 4. CHARACTERISTICS OF *CAMPYLOBACTER* OUTBREAKS REPORTED IN AUSTRALIAN AGED-CARE FACILITIES, 2001–2016

Transmission route	No. outbreaks (%)	No. cases (%)	No. lab-confirmed cases (%)	Median no. cases (min. to max.)	No. hospitalizations (total deaths)	Median outbreak duration in hours (min. to max.)
Unknown	10 (45.4)	82 (32.5)	35 (39.8)	6.5 (3 to 15)	3 (0)	72 (24 to 120) ^{a6}
Foodborne	8 (36.6)	143 (56.7)	40 (45.5)	14.5 (3 to 49)	10 (2)	72 (24 to 168) ^{a7}
Animal to person	2 (9.0)	16 (6.3)	6 (6.8)	8 (6 to 10)	1 (1)	144 ^{a1}
Waterborne	1 (4.5)	7 (2.8)	3 (3.4)	7 (–)	0 (0)	120 ^{a1}
Person to person	1 (4.5)	4 (1.6)	4 (4.5)	4 (–)	3 (0)	No data
Totals	22 (100.0)	252 (100.0)	88 (100.0)	8.5 (3 to 49)	17 (3)	96 (24 to 168) ^{a15}

^aNumber of outbreaks with data.

waterborne outbreaks ($n=5$), three occurred in camps, with single outbreaks in a child care center and an ACF. Rainwater tanks were identified as the source for four outbreaks, with a water bore the source for the fifth. Outbreaks involving person-to-person transmission were reported in an ACF, child care center, and private residence, whereas two outbreaks in a single ACF were linked to zoonotic transfer (Moffatt *et al.*, 2014).

Outbreaks were reported most frequently in ACFs, with 26% (22/84) occurring in this setting. Transmission source and associated disease burden for ACF outbreaks are given in Table 4. Among ACF outbreaks, 36% (8/22) involved foodborne transmission, whereas 45% (10/22) had an unknown transmission source. Foodborne outbreaks in ACFs were larger (median 14.5 cases) than those with an unknown transmission route (median 6.5 cases), whereas hospitalization frequency was significantly higher ($\chi^2=4.74$, $p=0.03$). Among foodborne outbreaks in ACFs, three-quarters (6/8) did not identify a food vehicle.

Examination of evidence levels obtained among the 73% (61/84) of outbreaks where a transmission route was determined showed 49% (30/61) utilized descriptive epidemiological evidence, 21% (13/61) statistical evidence, whereas 13% (8/61) used descriptive and statistical evidence in conjunction with microbiological findings. A further 10 outbreaks, including nine reported as foodborne, relied upon limited descriptive evidence, most often a common meal or restaurant exposure among cases but without a specific food vehicle being identified.

Data on food and environmental sampling conducted during investigations was available for 81 outbreaks, with 73% (59/81) of these investigations having no food or other samples collected for microbiological testing. For outbreaks involving sampling, 59% (19/32) yielded negative results, whereas 25% produced supportive evidence only (e.g., the presence of fecal indicator bacteria in a water sample). *Campylobacter* spp. were detected only four times in epidemiologically implicated foods, comprising chicken-liver pâté, duck livers, chicken wontons, and retail chicken meat. *Campylobacter* spp. was also recovered once from a rainwater tank supplying drinking water.

Investigators identified 57% (29/51) of foodborne outbreaks had one or more factors associated with pathogen contamination, whereas 47% (24/51) detailed factors relating to pathogen survival. Issues most frequently recorded were the ingestion of contaminated raw products intended to be cooked ($n=17$) and cross-contamination from raw ingredi-

ents ($n=14$), whereas for survival factors, insufficient temperature or cooking time was identified in 92% (22/24) of outbreaks. Most evidence used in determining contamination (83%, 24/29) and survival factors (71%, 17/24) were based on investigator assumption, as opposed to direct observation or measurement.

Discussion

Our study suggests that *Campylobacter* gastroenteritis outbreaks occur infrequently in Australia. Among outbreaks with recognized transmission sources, most were foodborne, with chicken or chicken-containing dishes the most commonly identified food vehicles. Although no rise in outbreaks over time was observed we did detect an increase in foodborne outbreaks involving poultry-liver. Other transmission sources seem to play a limited role in causing outbreaks in Australia. ACFs were the most frequently reported outbreak setting, whereas foodborne transmission occurred mostly in restaurants. A number of ACF outbreaks were reclassified to having an unknown transmission source, highlighting the challenges when gathering evidence to support inferences of foodborne transmission in that setting.

Despite robust food safety standards, Australia like many high-income countries, experiences significant disease burden because of *Campylobacter* spp. (Havelaar *et al.*, 2015; Moffatt *et al.*, 2017a). Despite this burden our results show a median of five outbreaks per year, with no increase in foodborne *Campylobacter* outbreaks as a proportion of all foodborne outbreaks over time. This infrequency of outbreaks relative to disease burden may be partly explained by *Campylobacter*'s innate physiology. Although invariably present on foods like raw poultry, the organism's fastidious growth requirements, coupled with sensitivity to environmental stressors limit its capacity to proliferate on food and survive cooking and freezing (Park, 2002). Similarly, international reporting shows *Campylobacter* contributes only a small proportion of the foodborne outbreak burden, although some increases are being reported. Between 2004 and 2008, the United States observed a two-fold increase (Geissler *et al.*, 2017), whereas in England the proportion of *Campylobacter* outbreaks increased significantly between 1992 and 2008, despite a decline in overall foodborne outbreaks (Gormley *et al.*, 2011). Such apparent differences with Australia could be attributed to variations in risk factors, transmission routes, surveillance and notification practices, or food regulation requirements.

Campylobacteriosis is recognized as a predominantly foodborne illness, with poultry being the major reservoir and the consumption and handling of poultry meat major risk factors (Skarp *et al.*, 2016). Globally, meat consumption has risen markedly over the past 20 years, driven largely by increases in poultry consumption, with Australians consuming >40 kg of poultry-meat per capita each year (Australian Bureau of Agricultural and Resource Economics and Sciences (ABARES) 2019). Consistent with this, our findings show a majority of outbreaks with a known transmission route were recorded as being foodborne, with chicken or poultry-containing meals the primary food vehicles. Although this study did not observe any increase in foodborne *Campylobacter* outbreaks *per se*, it did identify a significant increase in outbreaks linked to food vehicles such as pâté (Parry *et al.*, 2012; Moffatt *et al.*, 2016a), mirroring international outbreak reports implicating poultry-liver dishes (Little *et al.*, 2010; Lanier *et al.*, 2018). The ability of *Campylobacter* spp. to penetrate poultry livers through the hepatobiliary ducts (Whyte *et al.*, 2006), coupled with changes in eating habits and cooking practices (Jones *et al.*, 2016), provide a strong rationale for this observed increase.

Another food vehicle group responsible for outbreaks are unpasteurized dairy products. In the United States, these account for 69% of foodborne *Campylobacter* outbreaks (Geissler *et al.*, 2017), whereas we identified a single outbreak linked to unpasteurized milk, representing <2% of foodborne *Campylobacter* outbreaks. This discrepancy is explained by regulatory differences where in the United States, despite a federal ban on interstate commercial sales, numerous states permit sale of unpasteurized products within the state in which they were produced (Langer *et al.*, 2012). In contrast, Australia legally requires all milk and dairy products undergo pasteurization (or an equivalent process) to eliminate pathogenic microorganisms (Food Standards Australia and New Zealand (FSANZ), 2009), thus largely avoiding the issue.

Water sources are another recognized cause of *Campylobacter* outbreaks, with numerous large-scale events involving ground and surface water being reported throughout Europe, North America, and New Zealand (Moreira *et al.*, 2017). Although Australian estimates suggest 11% of campylobacteriosis cases are linked to water exposure (Gibney *et al.*, 2017), the majority of waterborne outbreaks have involved recreational exposure to *Cryptosporidium* infections (Dale *et al.*, 2010). Our study identified five waterborne outbreaks linked to drinking water, with four involving rainwater storage tanks and the fifth linked to bore water. Using rainwater tanks for household drinking water is common practice in Australia, particularly in rural and remote areas and the microbiological quality of such water is recognized as being less reliable (Environmental Health Committee (enHealth), 2011). Overall outbreak risk because of drinking water is probably low as a majority of Australians can access high-quality, regulated mains water; however, private supplies, particularly those utilizing rainwater storage tanks, carry some risk.

This study identified two outbreaks in an ACF involving probable zoonotic transmission through a puppy, highlighting a potentially emerging area of concern. Carriage and excretion of *Campylobacter* spp. in puppies and adolescent dogs is well-recognized (Hald *et al.*, 2004), whereas associ-

ations between human illness and puppy ownership have been demonstrated (Stafford *et al.*, 2007; Mughini Gras *et al.*, 2013). Although cognizant of the benefits of companion and therapy animals, the presence of puppies in such settings raises human health concerns (Moffatt *et al.*, 2014). Given our study has reported a number of ACF outbreaks without identified transmission sources we would encourage active efforts to exclude potential zoonotic transfer by scrutinizing age and species detail for all visiting or resident animals.

Our study shows ACFs to be the most common setting for *Campylobacter* outbreaks in Australia. Between 2001 and 2006, 18% (6/33) of outbreaks occurred in ACFs (Unicomb *et al.*, 2009), increasing to 26% (22/84) during our review period. Previously, *Campylobacter* spp. was shown to be the third highest cause of foodborne outbreaks in Australian ACFs (Kirk *et al.*, 2011). This contrasts with U.S. and UK data showing few foodborne aged-care outbreaks are attributed to *Campylobacter* spp. (Levine *et al.*, 1991; Ryan *et al.*, 1997). Such discrepancies could relate to a reporting bias, with all Australian states and territories requiring ACFs to report gastroenteritis outbreaks. Although this practice is well established in Australia, (Communicable Diseases Network Australia, 2010), potential underreporting of outbreak events should not be dismissed.

Although there are suggestions that higher rates of foodborne outbreak reporting in Australian ACFs may relate to more intensive investigation practices (Kirk *et al.*, 2012), our study shows a high proportion of these outbreaks lack evidence of foodborne transmission. Aged care is a challenging environment for investigations, with attempts to interview residents or retrospectively examine documentation leading to inconclusive findings (Winquist *et al.*, 2001). Our study shows food and environmental samples collected during outbreak investigations rarely result in *Campylobacter* spp. being detected, with this outcome in contrast to the relative successes achieved with trace-back sampling for *S. enterica* after egg-associated outbreaks in Australia (Moffatt *et al.*, 2017b). Given the proportion of ACF outbreaks with unknown transmission and their differing characteristics with outbreaks we have classified as foodborne, alternative transmission routes require consideration.

The Register has proved an invaluable tool in assisting varied public health and regulatory stakeholders with monitoring disease trends, developing policy and guiding food safety programs (Kirk *et al.*, 2008). We believe our liaison processes with states and territories, particularly requesting reviews of local records, have improved the quality of data presented, while addressing previous concerns regarding weak evidence and poor documentation of Register-derived data (Kirk *et al.*, 2011). A key aim of this study was to assess the quality of evidence used in assigning transmission routes, with the results showing that a number of outbreaks nominally recorded as being foodborne lacked the evidence to meet foodborne outbreak case definitions. Nevertheless differences in surveillance practices may have led to some foodborne outbreaks not being reported, with not all states and territories routinely contributing data to the Register until 2003. In addition, NSW only mandated the requirement to notify campylobacteriosis in 2017.

Public health capacity to routinely investigate even a small proportion of *Campylobacter* cases is currently constrained, with further difficulties imposed by the absence of a routine

subtyping system. However, a recent Danish study has shown whole genome sequencing may identify a higher degree of *Campylobacter* clustering and outbreak occurrence than previously thought (Joensen *et al.*, 2018). This illustrates the potential for this method as the basis for integrated surveillance routinely comparing human-derived isolates against those from established reservoirs. Although this could assist with detection of community-level outbreaks and the identification of sources within the primary production and processing sector, it remains possible that point-source foodborne outbreaks will remain uncommon because of *Campylobacter*'s physiology.

Conclusions

Campylobacter spp. remain a less commonly identified cause of gastroenteritis outbreaks in Australia. Although most outbreaks can be linked to foodborne transmission, including an increasing number caused by poultry-liver dishes, our study shows that gaps persist in evidence and knowledge around transmission. This is particularly evident for ACFs, where a higher frequency of outbreaks and an increased susceptibility of residents to poor health outcomes, mean efforts to better elucidate outbreak causes should be afforded a high priority.

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Address correspondence to:
Cameron R.M. Moffatt, MPH, MAppEpid
National Centre for Epidemiology and Population Health
Research School of Population Health
Australian National University
Acton 2601
Australia

E-mail: cameron.moffatt@anu.edu.au



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A large outbreak of *Campylobacter jejuni* infection in a university college caused by chicken liver pâté, Australia, 2013

C. R. M. MOFFATT^{1,2*}, A. GREIG³, M. VALCANIS⁴, W. GAO⁴, T. SEEMANN^{4,5},
B. P. HOWDEN^{4,6} AND M. D. KIRK²

¹ OzFoodNet, Communicable Disease Control, Health Protection Service, Australian Capital Territory Health Directorate, Canberra, Australia

² National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, Australia

³ Public Health Registrar, Communicable Disease Control, Health Protection Service, Australian Capital Territory Health Directorate, Canberra, Australia

⁴ Microbiological Diagnostic Unit Public Health Laboratory, Department of Microbiology and Immunology, The University of Melbourne at The Doherty Institute for Infection and Immunity, Victoria, Australia

⁵ Victorian Life Sciences Computation Initiative, The University of Melbourne, Victoria, Australia

⁶ Doherty Applied Microbial Genomics, Department of Microbiology and Immunology, The University of Melbourne at The Doherty Institute for Infection and Immunity, Victoria, Australia

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SUMMARY

In October 2013, public health authorities were notified of a suspected outbreak of gastroenteritis in students and guests following a catered function at a university residential college. A retrospective cohort study was undertaken to examine whether foods served at the function caused illness. A total of 56 cases of gastroenteritis, including seven laboratory-confirmed cases of *Campylobacter jejuni* infection, were identified in 235 eligible respondents. Univariate analysis showed a significant association with a chicken liver pâté entrée [relative risk (RR) 3.64, 95% confidence interval (CI) 2.03–6.52, $P < 0.001$], which retained significance after adjustment for confounding via multivariable analysis (adjusted RR 2.80, 95% CI 1.26–6.19, $P = 0.01$). *C. jejuni* and *C. coli* were also isolated in chicken liver pâté recovered from the college's kitchen. Subsequent whole genome multilocus sequence typing (wgMLST) of clinical and food-derived *C. jejuni* isolates showed three genetically distinct sequence types (STs) comprising ST528, ST535 (both clinically derived) and ST991 (food derived). The study demonstrates the value of utilizing complementary sources of evidence, including genomic data, to support public health investigations. The use of wgMLST highlights the potential for significant *C. jejuni* diversity in epidemiologically related human and food isolates recovered during outbreaks linked to poultry liver.

Key words: *Campylobacter*, molecular epidemiology, outbreaks, whole genome sequencing, zoonotic foodborne diseases.

INTRODUCTION

Campylobacter sp., are the most commonly reported cause of bacterial gastroenteritis worldwide and present as a significant challenge to public health and

* Author for correspondence: Mr C. R. M. Moffatt, National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, Australia, 2602.
(Email: cameron.moffatt@anu.edu.au)

food safety [1]. In Australia, campylobacteriosis is the most common enteric condition notified to health authorities, with a reported incidence of 101 cases/100 000 population in 2012 [2].

Infection with *Campylobacter* sp., usually results in an acute self-limiting gastroenteritis, characterized by diarrhoea and abdominal pain, with accompanying fever and symptoms such as general malaise and myalgia [3]. The incubation period is typically between 2 and 5 days, with illness duration lasting from several days to 2 weeks [3]. Transmission is predominantly regarded as being foodborne, with food production animals, especially poultry but also ruminant species being recognized as important reservoirs for human infection [4].

From a public health perspective, a noted feature of campylobacteriosis is the infrequency of outbreak events relative to disease incidence [5]. In recent years there has been an increase in published outbreak reports, particularly those linked to poultry-derived liver products such as pâté and parfaits [6–8]. At the same time the increasing availability of sequence-based typing and advances in bioinformatics have enabled greater insight into the characterization of *Campylobacter jejuni* [9]. However the potential for genomic diversity even in epidemiologically linked isolates requires further appreciation and carries potential implications for public health surveillance [7].

On 30 October 2013, a medical practitioner reported several cases of gastroenteritis in students from a university residential college, including one laboratory-confirmed case of campylobacteriosis. Contact with the college and rapid interviewing of unwell students identified a catered function as a potential source of illness.

METHODS

Epidemiological investigations

Initial interviewing of cases was conducted using a rapid hypothesis-generating questionnaire, which included a 3-day food history. Findings from these interviews revealed that all cases had attended a large catered function held at the college on the evening of 25 October 2013. A retrospective cohort study was undertaken to test the hypothesis that one or more foods served at this function were responsible for causing illness. Ethics approval was not sought as the investigation was conducted as part of a public health response.

Lists of function attendees and their contact details, including university email addresses and mobile

telephone numbers, were obtained via the residential college. A parallel environmental investigation was conducted that included interviewing of catering staff and sampling of residual foods. Interviews with function attendees were conducted by telephone using a standard questionnaire that captured details of symptoms, onset and exposure dates and times, and consumption of specific food and beverages based on the menu for the function.

A clinical case was defined as any person who attended the function on 25 October 2013 and subsequently developed signs or symptoms consistent with gastroenteritis, including diarrhoea, abdominal pain and/or vomiting between 26 October and 4 November 2013. Clinical cases were encouraged to provide a faecal sample to assist with the epidemiological investigation. A laboratory-confirmed case was defined as per a clinical case, in addition to having a faecal sample positive for *C. jejuni* subspecies *jejuni*.

Questionnaire data were entered into Microsoft Excel (Microsoft Corp., USA) for descriptive analysis and Stata v. 14 (StataCorp, USA) for univariate and multivariable analyses. Statistical analyses included the calculation of relative risks (RRs), adjusted relative risks (aRRs), associated 95% confidence intervals (CIs), and *P* values using a two-tailed Fisher's exact test. For the multivariable analysis, regression analysis was performed using a general linear model. A Wilcoxon rank sum test and a two-sample test of proportions were used to assess differences in age between cases and non-cases and differences in the proportion of male and female cases.

Microbiological investigations

Bacterial strains and identification/speciation

Campylobacter identification and speciation were confirmed by characteristic appearance on culture media, and testing for: oxidase, antibiotic susceptibility to nalidixic acid and cephalothin, and hydrolysis of hippurate [10]. Hippurate-negative strains were submitted for polymerase chain reaction assays for the detection of the hippuricase gene and the aspartokinase gene to identify *C. jejuni* and *C. coli*, respectively [11].

Whole genome sequencing (WGS) and bioinformatics analysis

WGS and comparative genomics were applied to human and food-derived outbreak isolates to determine the sequence-level similarities of the epidemiologically

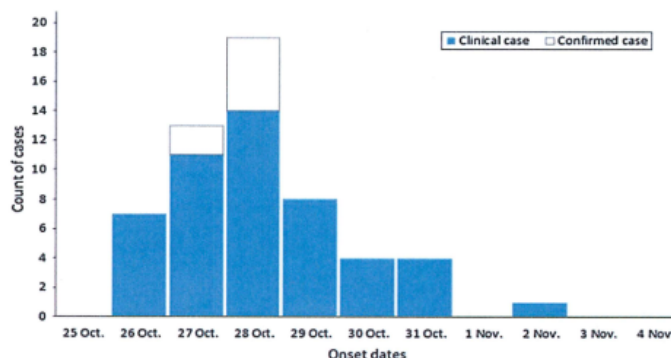


Fig. 1. *Campylobacter*-associated gastroenteritis cases by date of onset, Australia, October and November 2013 ($n = 56$).

linked *C. jejuni* cases and food isolates, as we hypothesized that significant variability could be found in epidemiologically linked cases.

After extraction of genomic DNA, sequencing libraries were created using the Nextera XT DNA preparation kit (Illumina, USA). Sequencing was performed on the NextSeq 500 platform with 150-bp paired-end chemistry. The sequenced reads were mapped to the complete *C. jejuni* reference sequence RM1221 (NCBI accession no. NC_003912.7), and single nucleotide polymorphisms (SNPs) were detected using Snippy v. 3.0 (<https://github.com/tseemann/snippy>), with a minimum mapping coverage threshold of 10 and a base-call stringency of 90%. A phylogenetic tree was constructed using core genome SNPs using FastTree v. 2.1.8 [12]. The multilocus sequence type (MLST) was inferred *in silico* from assembled WGS reads using MLST v. 2.0 (<https://github.com/tseemann/mlst>).

RESULTS

Epidemiological investigations

Descriptive results

A total of 269 persons were identified as having attended the function on 25 October 2013. Of these, 87% (235/269) were interviewed as part of the cohort study. In total, 56 clinical and laboratory-co-confirmed cases of gastroenteritis were identified in the study respondents, giving an attack rate of 24% (56/235). Included in these cases were seven persons with microbiologically confirmed *C. jejuni* infection. Faecal samples were collected between 3 and 7 days after

the function with a median incubation period of 61 h (range 39–74 h) in those providing samples. The epidemic curve (Fig. 1) shows the onset dates for clinical and confirmed cases, with a median incubation time of 61 h (range 5–188 h). Duration of illness was not calculated as most cases were symptomatic at the time of questionnaire completion. There was no statistically significant difference in age between cases and non-cases ($P = 0.37$), nor in the proportion of male and female cases ($P = 0.28$). The most frequently reported symptoms were diarrhoea (82%), abdominal pain (79%), nausea (61%), and fever (59%). Eighteen cases reported visiting a general medical practitioner, including one who presented to a hospital emergency department. No hospital admissions were reported.

Analytical results

Table 1 shows the results for the univariate epidemiological analysis. Increased risk of illness was shown for chicken liver pâté being eaten as an entrée (RR 3.64 95% CI 2.03–6.52, $P < 0.001$). An inverse association with illness was demonstrated if the alternative entrée option, the beetroot salad, had been consumed (RR 0.51 95% CI 0.31–0.83, $P = 0.005$). Following multivariable analysis only the chicken liver pâté retained statistical significance as an exposure variable (aRR 2.80, 95% CI 1.26–6.19, $P = 0.01$).

Chicken liver pâté preparation

On 31 October, the kitchen was inspected and leftover pâté samples were collected. An interview with the catering manager revealed that the pâté had been prepared by an agency chef, using a new recipe. The pâté

Table 1. Relative risks for food exposures following a *Campylobacter jejuni* outbreak, Australia, October 2013

Menu item	Exposed			Unexposed			RR	95% CI	P value
	No. ill	Total no.	AR (%)	No. ill	Total no.	AR (%)			
Cold canapés	36	131	27.48	20	104	19.23	1.43	0.88–2.31	0.14
Hot canapés	19	75	25.33	37	160	23.13	1.10	0.68–1.77	0.71
Any canapés	38	147	25.85	18	88	20.45	1.26	0.78–2.07	0.35
Chicken liver pâté with port wine jelly and crostini	44	118	37.29	12	117	10.26	3.64	2.03–6.52	<0.001
Baby beet salad with micro herbs and feta	19	118	16.10	37	117	31.62	0.51	0.31–0.83	0.005
Any entrée	54	208	25.96	2	27	7.41	3.50	0.91–13.56	0.03
Spatchcock with Dutch carrots and red wine jus	31	111	27.93	25	124	20.16	1.39	0.87–2.20	0.16
Moroccan lamb on rosti with onion jam and glaze	36	137	26.28	20	98	20.41	1.29	0.80–2.08	0.30
Vegetarian main meal option	2	15	13.33	54	220	24.55	0.54	0.15–2.01	0.32
Any main meal	55	226	24.34	1	9	11.11	2.19	0.34–14.10	0.36
Rose brûlée with biscotti	30	107	28.04	26	128	20.31	1.38	0.87–2.18	0.17
Chocolate marquise with raspberry	33	135	24.44	23	100	23.00	1.06	0.67–1.69	0.80
Any dessert	50	195	25.64	6	40	15.00	1.71	0.79–3.71	0.15

AR, Attack rate; RR, relative risk; CI, confidence interval.

preparation began 2 days prior to the function, with the chicken livers being soaked in milk and then left overnight in a cool room. The following day they were drained and sautéed in a pan, along with onion, garlic butter and port wine. The livers were described as being 'medium cooked', having a slightly pink inside. A temperature probe was not used to assess their internal temperature following this cooking step. The livers were then seasoned and blended, before a mixture of clarified butter and vegetable oil was added. The pâté mixture was then transferred to moulds and placed in a cool room. The pâté remained in the cool room until ~30 min prior to dinner service.

Microbiological investigations

Eight stool samples were obtained from cases, with seven being culture positive for *C. jejuni* subspecies *jejuni*. Four isolates from chicken liver pâté underwent confirmation, speciation and molecular analysis. Two were identified as being *C. jejuni* and two as *C. coli*. All environmental swabs taken from the kitchen on 31 October 2013 were negative for *Campylobacter* sp., *Salmonella* sp. and *Escherichia coli*.

To further define the relationship between human and food isolates of *C. jejuni*, nine isolates underwent WGS and phylogenetic analysis (Fig. 2). This

demonstrated three distinct clusters of isolates (five case isolates of MLST ST528 *C. jejuni*) that differed by a maximum of eight SNPs from each other, two ST535 case isolates that differed by 30 SNPs, and two ST991 pâté isolates that differed by 65 SNPs. The WGS analysis confirmed that the human case isolates were genetically distinct from the food isolates (Table 2).

DISCUSSION

Our epidemiological analysis demonstrated that chicken liver pâté, served as an entrée, was the food vehicle responsible for an outbreak of campylobacteriosis at a university college. We found a significant association between consuming chicken liver pâté and development of gastroenteritis. This finding was supported by microbiological evidence yielding *C. jejuni* in clinical specimens and the recovery of both *C. jejuni* and *C. coli* from leftover pâté sampled from the residential college's kitchen. Further, the food safety investigation determined that the chicken livers used in the pâté had likely been prepared in a manner that would have allowed *Campylobacter* sp. to survive the cooking process.

The epidemiology of campylobacteriosis in industrialized countries is characterized by the infrequency of reported outbreaks relative to the overall incidence

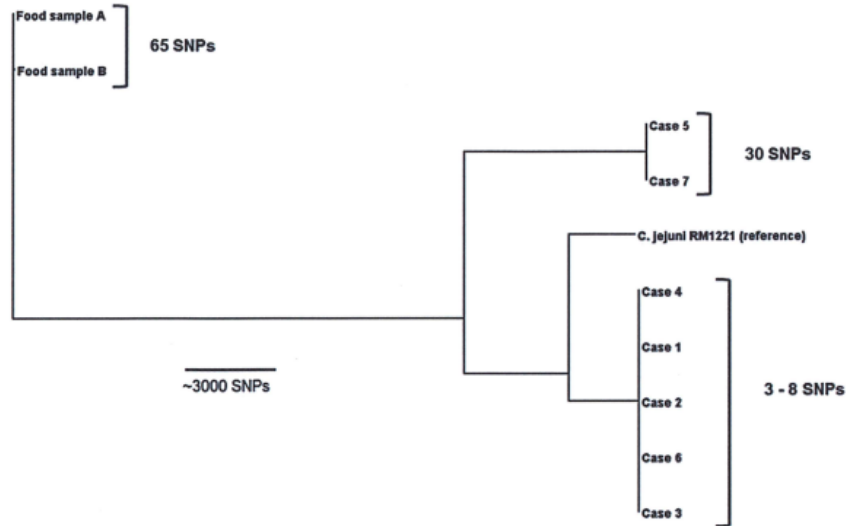


Fig. 2. Phylogenetic tree of nine *Campylobacter jejuni* outbreak isolates based on core-genome single nucleotide polymorphisms (SNPs), Australia 2013.

Table 2. Core single nucleotide polymorphism distances between *Campylobacter jejuni* clinical and food outbreak isolates, Australia, October 2013

Identifier	Pâté sample A	Pâté sample B	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Reference
Pâté sample A	0	65	22 944	22 940	22 943	22 942	23 241	22 941	23 242	22 924
Pâté sample B	65	0	22 957	22 953	22 956	22 955	23 262	22 956	23 263	22 943
Case 1	22 944	22 957	0	4	7	8	13 123	5	13 130	5004
Case 2	22 940	22 953	4	0	5	6	13 121	3	13 126	5002
Case 3	22 943	22 956	7	5	0	7	13 122	4	13 127	5005
Case 4	22 942	22 955	8	6	7	0	13 121	5	13 126	5004
Case 5	23 241	23 262	13 123	13 121	13 122	13 121	0	13 122	30	12 847
Case 6	22 941	22 956	5	3	4	5	13 122	0	13 127	5003
Case 7	23 242	23 263	13 130	13 126	13 127	13 126	30	13 127	0	12 847
Reference	22 924	22 943	5004	5002	5005	5004	12 847	5003	12 847	0

of disease [5, 13]. When outbreaks do occur, the types of food vehicles that are implicated have been shown to vary internationally, with Australia identifying chicken meat as a major food vehicle [5], while elsewhere dairy products, particularly raw milk, and untreated drinking water have been identified as causes of outbreaks [13, 14]. Commentary on the increase in outbreaks of campylobacteriosis linked to offal, specifically poultry livers [15, 16] supports the establishment of liver pâté and similar dishes, as an increasingly important food vehicle during such events.

One factor potentially contributing to the apparent increase in liver-associated campylobacteriosis outbreaks is a change in consumer eating habits, with consumption of raw and minimally cooked foods gaining more widespread acceptance [17]. Such a trend has perhaps evolved without sufficient awareness or understanding of potential risks associated with raw or minimally cooked foods, as evidenced by the increasing number of outbreaks of salmonellosis linked to foods containing raw eggs in Australia [18]. While poultry production and consumption has soared in Australia

it remains difficult to obtain data describing domestic offal consumption, although it is reported that 95% of Australian chicken offal is exported [19].

The relative infrequency of outbreaks due to *Campylobacter* sp., compared to outbreak-prone foodborne pathogens, such as *Salmonella* sp., creates a significant challenge in highlighting and maintaining awareness in consumers, restaurants and the catering sector of risks associated with poultry-liver use. *C. jejuni* in particular, is a prolific surface contaminant of poultry meat but the organism's inherent susceptibility to heat suggests that effective cooking practices will kill most organisms, leaving cross-contamination as a more likely mechanism for infection [20, 21]. Pâté, however, represents one of the few food vehicles where internal contamination of the liver tissue is likely and undercooking can result in campylobacteriosis. [22]. For poultry livers used in pâté to be free of *Campylobacter*, they need to be held at an internal temperature $>70^{\circ}\text{C}$ for 2–3 min [22]. However, an important consideration for those preparing pâté is ensuring that cooked livers retain 'pinkness', a feature regarded as being desirable to consumers; if cooked too long the livers will become grey, with their flavour and texture being compromised [22]. The use of such subjective measures to determine the readiness of cooked poultry liver could potentially result in the occurrence of an outbreak situation such as we have described.

Our results revealed a high degree of difference between the two human outbreak-associated sequence types, as well as distinct differences between these and the sequence type found in the pâté recovered from the kitchen. Despite the absence of a definitive genetic link between the clinical and food isolates, we do not believe this adversely impacts our investigation's conclusion that *Campylobacter*-contaminated chicken liver pâté was responsible for this outbreak. The small differences in SNPs in cases with the same sequence type, suggests a common source and further supports the closeness of the epidemiological association we have outlined.

Our findings also align with other studies employing molecular typing of outbreak isolates where recovery of differing *C. jejuni* strains from epidemiologically linked cases has been demonstrated [7, 23]. In this investigation, cases within the two distinct groups differed by more than 13 000 SNPs. Explanations for such differences in cases during outbreaks could include strain diversity at the reservoir level [24], and the impact of cross-contamination and strain mixing during

slaughtering and processing [25] or at wholesale or retail sale points [26]. The microbiological processing of food samples in the laboratory may also not have uncovered the full genetic diversity within the source.

While there are a limited number of studies concerning *C. jejuni* MLST from patients from different parts of the world, the predominant lineages appear to show some regional differences [27]. Interrogation of the *Campylobacter* MLST website shows that both ST528 (CC354) and ST535 (CC460) have been identified previously with sporadic human infection in Australia, with a suggestion that ST528 may be endemic [28]. ST535 appears to have a more global distribution, with sporadic cases reported from Canada, Japan, Germany Thailand and the UK (PubMLST, accessed October 2015), further illustrating the complexities of *C. jejuni*'s genetic epidemiology.

While MLST has been demonstrated to be a good predictor of the genome-level relatedness of *C. jejuni* isolates [29], the interpretation of outbreak-associated isolates, including the integration of epidemiological data with SNP differences, is less well established [30]. Examples, however, do include the investigation of outbreaks linked to improperly pasteurized milk and contaminated drinking water [30, 31], highlighting differing levels of genomic diversity in outbreak strains, presumably due to the transmission routes and underlying reservoirs. We believe our investigation is the first use of WGS to aid characterization of a *C. jejuni* outbreak caused by contaminated poultry liver, with our results supporting previous findings showing marked strain diversity in isolates linked to foodborne poultry liver outbreaks [7, 32]. However a dearth of local data describing common sequence types from clinical cases and reservoirs particularly poultry, presently limits our interpretations and understanding of the genetic epidemiology of campylobacteriosis in Australia.

A strength of our investigation was the high response rate in attendees (87%), underscoring the validity of our conclusion that liver pâté was the food vehicle responsible for this outbreak. We were able to commence interviews within 6 days of the implicated function, with the majority of respondents' details collected over the following four working days. Contributing to this success was the agreement by the college to provide student mobile phone and email details, enabling contact via multiple communication media. With respect to bias, the closed setting and interconnectedness of students could have introduced ascertainment bias. However, our finding of

an inverse association with illness and consumption of the alternate entrée option, suggests such an effect to have been unlikely. Similarly, recall bias is another potential issue, with students served the pâté potentially reporting this exposure differently to students who were served the alternate entrée but who may have then swapped this or otherwise sampled the pâté. Despite the common exposure, case misclassification also remains a possibility, with only 14% (8/57) of cases submitting stool samples for culture.

CONCLUSIONS

Poultry-liver-derived dishes, such as pâté and parfait, have become established food vehicles during outbreaks of campylobacteriosis. We believe this study represents the first use of WGS to aid characterization of a *C. jejuni* outbreak caused by contaminated poultry liver, and highlights the potential genetic diversity in epidemiologically linked food and human isolates. The study highlights the usefulness of employing complementary components of epidemiological evidence, including genomic data, to support public health inference.

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DECLARATION OF INTEREST

None.

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Chapter 4 *Campylobacter*-associated hospitalisation



Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppi/document/ANUP_003405

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Manuscript 4

Title: *Campylobacter*-associated hospitalisations in an Australian provincial setting. _____

Authors: Moffatt, CR, Kennedy, KJ, Selvey, L, Kirk MD. _____

Publication outlet: *BMC Infectious Diseases* _____

Current status of paper: Published

Contribution to paper: The candidate conceived the study design, undertook data collection and analysis and drafted the manuscript

Senior author or collaborating authors endorsement: MD Kirk

Manuscript 5

Title: Bacteraemia, antimicrobial susceptibility and treatment among *Campylobacter*-associated hospitalisations in the Australian Capital Territory. _____

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Manuscript 6

Title: First case report of myopericarditis linked to *Campylobacter coli* enterocolitis _____

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Australian
National
University

CAMERON MOFFATT

Candidate – Print Name

Cameron Moffatt

Signature

17/12/20

Date

Endorsed

Professor Martyn Kirk

Primary Supervisor – Print Name

MD Kirk

Signature

29/12/2020

Date

Cathy Banwell

Delegated Authority – Print Name

Cathy Banwell

Signature

3/01/2021

Date

In this chapter I examine clinical outcomes and the potential for severe disease under the theme of *Campylobacter*-associated hospitalisation. Arguably the need for hospital admission can be viewed as a marker for disease severity, with this theme being examined through three manuscripts that draw upon retrospectively collected public hospital data from the ACT between 2004 and 2013. The first manuscript provides a description of processes undertaken to accurately determine *Campylobacter*-associated hospitalisations, along with a detailed review of the clinical and epidemiological characteristics of the inpatient cohort. The second manuscript examines factors associated with blood culture collection, bacteraemia, antibiotic treatment and isolate non-susceptibility to standard antimicrobials among the hospitalised cohort. The third and final manuscript utilises a case report approach to describe the presentation and management of a novel case of myopericarditis identified during the review of *Campylobacter*-associated admissions.

Hospitalisation is an important clinical outcome when assessing the severity of foodborne and other enteric infections, including campylobacteriosis [1]. As previously noted in Chapter 2, Australia's state and national disease surveillance systems, along with those in many other high-income settings, are typically passive and capture limited data on severity of disease markers like hospitalisation and mortality [2, 3]. Use of hospitalisation data to identify cases admitted with foodborne and enteric infections can also be problematic, due to issues with the accuracy of pathogen specific diagnoses and morbidity coding [4]. Registry-based data linkage and case control studies show hospitalisation rates to be around 10% [1, 5] but examples where hospitalisation data are routinely incorporated with surveillance reporting remain limited [6]. To address issues in settings where data are not routinely linked, the development of estimates for the numbers of hospitalisations has become a conventional aspect of describing foodborne and enteric disease-related burden in high-income settings [2, 7, 8].

Given the increased awareness of *Campylobacter*'s epidemiology, including higher rates of male disease, age-related risk, increasing incidence and increased non-susceptibility to antimicrobials, it is important to have an understanding of potential impacts upon health outcomes like hospitalisation. Current data describing the clinical characteristics of hospitalised cases in Australia is scarce, with earlier data (circa 30 years prior) being derived from a single specialist infectious disease hospital [9] or through small case series involving specific complications like bacteraemia [10]. Elsewhere internationally, large reviews of case presentation and management appear to have been last undertaken at a time when *Campylobacter* spp. were viewed as emerging pathogens [11], although contemporary data describing case characteristics for complications like bacteraemia are more readily available [12, 13].

In view of this background, the aims of the first manuscript presented in this chapter are to accurately quantify counts of *Campylobacter*-associated hospitalisations within a well-defined population and to provide a contemporary insight into the characteristics of hospital admissions to strengthen understanding around disease burden and severity. This work also aids in validating previous Australian hospitalisation estimates for foodborne and enteric pathogens [7] as well as establishes a basis for future exploration of *Campylobacter* infection and hospitalisation.

The dataset used in the analysis of *Campylobacter*-associated hospitalisations described in this Chapter was constructed through the linkage of public hospital administrative and laboratory datasets, along with data derived from a retrospective review of individual patient medical records. A detailed description of these methods, along with an accompanying flow diagram are included in the first manuscript contained within this chapter (see Figure 1).

Through access to hospital laboratory data, it was possible to identify admission episodes where *Campylobacter* spp. had been isolated from a clinical specimen, giving an indication

of total numbers of *Campylobacter*-associated hospitalisations. This allowed for assessment of underreporting associated with hospital-generated morbidity data. Although a number of measures of ‘diagnostic accuracy’ are presented in the findings of the manuscript, sensitivity is the most useful measure to assess underreporting as morbidity coding outcomes are being compared against the “gold standard” of laboratory-confirmed *Campylobacter* infection. From a disease surveillance perspective, sensitivity refers to the proportion of cases (or health-events) that are detected by a system and can be calculated using the formula $\text{True Positive} / (\text{True Positive} + \text{False Negative})$ [14]. For this study *True Positive* refers to admissions with laboratory-confirmation of *Campylobacter* infection and an accompanying primary or secondary International Classification of Diseases (ICD) code A04.5 *Campylobacter* enteritis. *False Negative* refers to those admissions with laboratory confirmation but an absence of the ICD code A04.5. The sensitivity results presented can therefore be interpreted as the ability of hospital morbidity coding to correctly assign a *Campylobacter* diagnosis to an admission when *Campylobacter* spp. has been isolated from a clinical specimen.

Descriptions of other statistics used in this study are provided in the Methods section of the manuscript, although it is important to note that non-parametric statistical methods were favoured due to the underlying distribution of key continuous data including age, length of stay (LOS), Charlson Comorbidity Score [15] and time to admission. These data failed to meet the requirements of conventional parametric methods as they were non-normally distributed and contained significant outliers [16]. LOS data, for example, tends to have a rightward skew due to a minority of patients with disproportionately long admissions [17].

Campylobacteriosis most commonly presents as a self-limiting enterocolitis, with secondary bacteraemia a clinically important but relatively infrequent complication [18]. Within high-income settings the population-level incidence of *Campylobacter* bacteraemia has been

reported as <0.50 cases per 100,000 population [12, 19]. However there is a view that many cases of *Campylobacter* bacteraemia remain undetected due to their transient nature or because of protocols within microbiology laboratories regarding incubation periods for blood collection bottles [20]. The gold standard for diagnosing bacteraemia is a blood culture [21], however predicting whether a case will develop bacteraemia is challenging, with the pre-test probability dependent upon the clinical context and source of infection [22]. While signs such as fever are often a common prompt [22] ordering of blood cultures in the context of acute enterocolitis is less common [18]. Among host factors associated with *Campylobacter* bacteraemia, older age and higher levels of comorbidity such as liver disease and immunosuppression have been identified [19].

Antimicrobial therapy is not routinely recommended for campylobacteriosis, although it may be advised for patients with or at risk of severe disease [23]. There is little detailed data available on rates of antibiotic prescribing among either community or hospitalised *Campylobacter* cases, although Australian estimates for *acute gastroenteritis* cases suggest around 5% receive antibiotics [24]. For hospitalised cases with confirmed *Campylobacter* infection, prescribing rates could be expected to be higher. However a threat to effective prescribing are the increasing rates of non-susceptibility among *Campylobacter* clinical isolates in high-income countries, particularly resistance to fluoroquinolones [25]. By comparison, significantly lower rates of ciprofloxacin non-susceptibility among *Campylobacter* isolates have previously been reported in Australia [26]. For high-income settings, international travel remains the most significant risk factor associated with isolate non-susceptibility [27, 28].

In the second hospitalisation manuscript, the principal analyses involved the use of logistic regression to examine explanatory factors associated with blood culture collection, bacteraemia, antibiotic treatment and isolate non-susceptibility to standard antimicrobials.

Given this methodological focus it is important to provide some further rationale and justification. Multivariable logistic regression is most commonly used for the analysis of multiple independent (i.e. explanatory variables) in relation to a single binary outcome [29]. While the outcome variables in the models were binary, the logistic regression equation does not predict the outcome of the binary variable but rather the probability of the outcome. This requires transformation of the binary data into a linear form via a logit function [29]. The regression process then identifies the strongest linear combination of variables with the greatest probability of detecting the observed outcome, a method known as maximum likelihood estimation [29].

Development of the models presented in the second manuscript involved a number of considerations, including selection of explanatory variables, assessment of underlying statistical assumptions, choice of model building strategy and the goodness-of-fit for each model [29]. Clinical and epidemiological judgement were drawn upon when considering variables that included age, gender, country of birth, previous hospitalisation, overseas travel history, signs and symptoms associated with enterocolitis, derangement of vital signs, comorbidities and admitting clinical units. Variable selection was further aided by univariate analysis that provided estimated relative risks (RRs), 95% confidence intervals (CIs) and *p*-values. Those variables with univariate test results that included a *p*-value < 0.20 were considered in the models, with this cut-off chosen due to traditional levels such as $p \leq 0.05$ potentially failing to identify important variables [30]. Conversely it should be noted that use of a higher cut-off could lead to the inclusion of variables of questionable value, hence the deferment to non-automated, clinical and epidemiological judgment in final variable selection as described further below.

The underlying statistical assumptions considered when undertaking a logistic regression, include use of binary outcomes, independence of observations, linearity in the logit for

explanatory variables, absence of multicollinearity and sample size [29]. In the models presented in the study all outcome variables were in a binary format to enable a logistic regression analysis to be conducted. Binary outcomes were also recorded for independent variables, thereby ensuring they were linearly related to the log odds. Independence of individual observations was aided by the 10 year study period, coupled with the sporadic nature of most *Campylobacter* infections. Collinearity was assessed through review of the variance inflation factor (VIF) and tolerance. The VIF indicates how much inflation of the standard error could be caused by collinearity, while tolerance indicates how much collinearity the regression analysis can accept. If the variables have no correlation with each other, the VIF and tolerance will be 1. If a variable is closely related to another variable(s), and the VIF becomes very large, the tolerance goes to 0. Collinearity diagnostics showed no issues with multi-collinearity. The mean VIF and range of tolerances for each of the models were as follows: blood specimen collection model (VIF 1.32, tolerance 0.54 – 0.96), positive blood culture model (VIF 1.06, tolerance 0.87 – 0.98), ciprofloxacin non-susceptibility model (VIF 1.05, tolerance 0.92 – 0.99), any non-susceptibility model (VIF 1.04, tolerance 0.93 – 0.98) and the antibiotic treatment model (VIF 1.26, tolerance 0.61 – 0.97). Finally logistic regression typically requires a large sample size. While the study data were collected from a 10 year period, a number of different outcomes were modelled. Some, including isolation of *Campylobacter* spp. from blood, are not common events and would require significantly larger source populations in order to achieve adequate sample sizes. This issue is identified as a limitation in the second manuscript, specifically in the context of imprecision of model estimates.

The statistical approach to model building involves minimizing the number of variables to ensure the resulting model is numerically stable, as more variables lead to increases in the estimated standard error [30]. In contrast, the epidemiological approach to model building

advocates the inclusion of all relevant variables in a model, with the aim of controlling for the effects of confounding [31]. To accommodate these approaches, a manual, stepwise building strategy was used. This is a modification of forward selection where variables are added one at a time, beginning with the most significant explanatory variable as determined by univariate screening and investigator consensus. With each addition of an explanatory variable to the model, a likelihood ratio test was applied to see if the variable's significance was reduced below a specified alpha-level, in this case $\alpha = 0.05$. If the potential explanatory variable was identified as being non-significant it was removed from the model, with this process repeated for all candidate variables until a final model was reached.

Goodness-of-fit testing is a method of determining how well a model fits the sample data [29]. For logistic regression models, the Hosmer and Lemeshow goodness-of-fit test is a well-established and widely used summary statistic for model fit [30]. This test involves dividing sample observations into equal groups based on their estimated probability of having the outcome of interest. If the model has good fit, subjects who experienced the outcome should be placed into the higher risk groups. A poorly fitted model would result in observations being evenly spread among the risk groupings for both binary outcomes [29]. It is computed as the Pearson chi-square from the contingency table of observed frequencies and expected frequencies, with a good fit yielding a large p -value [32]. The Hosmer and Lemeshow goodness of fit statistics for each model are included in Tables 2-6 of the second manuscript.

The final manuscript included in the chapter is a case report. Case reports are detailed descriptions of one or a few clinical cases involving an unusual disease or complication [33]. While unable to measure disease risk or frequency they can still be beneficial in drawing attention to emerging or rare clinical events as well as contribute to the development of hypotheses used in larger clinical or epidemiological studies [33]. Acute pericarditis refers to

inflammation of the pericardium, a thin fluid-filled sac that surrounds the heart, with the term myopericarditis used to describe additional inflammation involving the myocardium [34]. In high-income settings, most pericarditis and myopericarditis cases are regarded as being idiopathic, while those thought to be of an infectious origin are generally attributed to viruses [34]. The epidemiology of *Campylobacter*-associated myopericarditis suggests it is relatively uncommon, with disease occurring predominantly in younger, healthy males, and with involvement of a single causative species, *C. jejuni* [35]. More recently there has been an increasing number of pericarditis and myopericarditis cases documented as complications following *Campylobacter* infection [36].

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RESEARCH ARTICLE

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Campylobacter-associated hospitalisations in an Australian provincial setting

Cameron R. M. Moffatt^{1*}, Karina J. Kennedy², Linda Selvey³ and Martyn D. Kirk¹



Abstract

Background: *Campylobacter* spp. infections are a globally important cause of enterocolitis, causing substantial morbidity. Capturing accurate information on hospitalisations is challenging and limited population-level data exist to describe the clinico-epidemiological characteristics of hospitalised cases.

Methods: Hospital administrative and laboratory datasets were linked to identify *Campylobacter*-associated hospitalisations between 2004 and 2013. Accuracy of morbidity coding was assessed using laboratory diagnosis as a gold standard, with health department surveillance data used to calculate population-based rates. Additional patient-level data were collected via review of medical records. Descriptive statistics were used to assess changes in rates and proportions and to assess relationships between key variables including age, length of stay, comorbidity and complications.

Results: In total 685 *Campylobacter*-associated hospital admissions were identified, with the sensitivity of morbidity coding 52.8% (95% CI 48.9–56.7%). The mean annual rate of hospitalisation was 13.6%. Hospitalisation rates were higher for females across most age-groups, while for both genders marked increases were observed for those aged ≥ 60 years. Median admission age was 39.5 years, with an average length of stay of 3.5 days. Comorbidities were present in 34.5% (237/685) of admissions, with these patients more likely to develop electrolyte disturbances, hypotension, renal impairment or acute confusion (all $p < 0.001$). Bacteraemia and acute kidney injury were observed in 4.1% (28/685) and 3.6% (23/685) of admissions, respectively. Inpatient mortality was low (0.15%).

Conclusion: Under reporting of *Campylobacter*-associated hospitalisations is substantial but can be improved through data linkage. We observed demographic differences among those hospitalised but further work is needed to determine risk factors and predictors for hospitalisation.

Keywords: *Campylobacter*, Infectious gastroenteritis, Hospitalisation, Length of stay, Comorbidity, Epidemiology, Clinical coding, Data accuracy

Background

In high-income settings, *Campylobacter* spp. are the most frequently reported bacterial enteric pathogen, with increasing disease incidence observed in the United States (US), European Union and Australia [1–3]. *Campylobacter*iosis typically presents as an acute enterocolitis, characterized by profuse diarrhoea and abdominal pain, along

with nonspecific symptoms including fever, myalgia and lethargy [4]. While uncommon, complications including bacteraemia and post-infectious sequelae such as reactive arthritis and Guillain-Barré syndrome also occur [5–7].

National (and provincial-level) enteric surveillance systems are frequently passive, capturing only limited data on outcomes such as hospitalisation and death [8]. Consequently, estimating hospitalisation has become an established method for describing foodborne-related disease burden [8–10]. Nevertheless, differences in data sources and the assumptions underpinning these methods make

* Correspondence: cameron.moffatt@anu.edu.au

¹National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, ACT 2602, Australia

Full list of author information is available at the end of the article



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intercountry comparison of hospitalisation rates challenging [8].

Given increasing disease incidence and concerns regarding accuracy of estimates, it is important to re-examine *Campylobacter*, with the aim of this study to quantify associated hospitalisations and describe their epidemiological and clinical characteristics, including the spectrum of illness, risk factors and associated outcomes.

Methods

Setting

The Australian Capital Territory (ACT) is a self-governing territory in south-eastern Australia, surrounded by the state of New South Wales (NSW). It contains the national capital Canberra, with an estimated population of 410,000 [11]. Two public hospitals service the ACT. Canberra Hospital, an acute care teaching facility of approximately 600 beds, acts as the tertiary referral centre to both the ACT and surrounding parts of NSW, while Calvary Public Hospital, is a smaller acute care teaching facility of approximately 250 beds. Both hospitals support around 550,000 people in the ACT and surrounding NSW. Three private hospitals operate within the ACT but only the two public hospitals have emergency departments (EDs).

Outcome definition and objectives

A *Campylobacter*-associated admission was defined as any inpatient episode clinically and temporally linked to a hospital-derived *Campylobacter* isolate. Our study objectives included examining admission counts and calculating hospitalisation rates, describing the clinical and demographic characteristics of admissions and assessing the impact of admission characteristics, including age, gender and comorbidity, on outcomes including length of stay (LOS) and time to admission.

Data sources and data collection

Hospital administrative data

We obtained public hospital admissions data between 01 January 2004 and 31 December 2013, where the International Classification of Diseases (ICD) morbidity code 'A045 *Campylobacter* enteritis' was recorded as a primary or secondary diagnosis. Included were unit record (UR) and admission numbers, birth dates, gender, admission and discharge dates, admission sources, admission units and discharge destinations. LOS was calculated by subtracting admission from discharge dates, with reporting in whole days. Same day admissions and discharges received a LOS of 1 day. Private hospital admissions were not sought due to the acute nature of campylobacteriosis and absence of private hospital EDs.

Hospital microbiology data

Hospital microbiology data for the period 01 January 2004 to 31 December 2013 were used to identify admissions where *Campylobacter* spp. were isolated from clinical samples but where ICD code 'A045' was not assigned. UR and admission numbers, birth dates, gender, isolation dates, specimen type (e.g. faeces, blood), and hospital, ward and unit identifiers were provided, facilitating linkage with administrative data. All *Campylobacter* diagnoses were made via culture, with routine speciation not performed before 2013. Details on concurrent isolation or detection of additional enteric pathogens were also provided.

Medical record data

Medical records were reviewed to confirm admissions and retrieve details unavailable via administrative data sets. This included the presence or absence of signs and symptoms, onset dates (defined as the date of earliest diarrhoea), time to admission (defined as difference in whole days between the onset and admission date), travel history, comorbidities, complications and discharge summaries. Time to admission was calculated for initial acute admissions and not for readmissions or inter-state hospital transfers.

Key signs of infection sought included tachycardia (resting heartrate ≥ 110 bpm), hypotension (systolic blood pressure < 90 mmHg), electrolyte imbalance (levels outside of typical reference range for serum sodium of 135–145 mmol/L and/or potassium of 3.5–5.2 mmol/L) and acute renal impairment (levels above typical reference range for serum creatinine in males of 60–110 μ mol/L and females of 45–90 μ mol/L and/or urea of 3.0–8.0 μ mol/L). Charlson Co-morbidity Index (CCI) scores [12] were calculated as a marker of comorbidity.

ACT surveillance notifications and emergency presentation data

Campylobacter notification data between 01 January 2004 and 31 December 2013 were obtained from the ACT Government Health Directorate. After identifying ACT resident *Campylobacter*-associated admissions, we sought to link these back to notification data using birth date, gender, postcode and specimen collection date. This enabled calculation of a hospitalisation rate for ACT campylobacteriosis cases. Hospital-generated microbiology data also enabled matching of non-admitted ED presentations to notification data to calculate an ED presentation rate for ACT residents.

Exclusions

Admissions were excluded if additional enteric pathogens were detected or isolated from a sample, if diarrhoeal symptoms commenced ≥ 48 h after admission and

if *Campylobacter* spp. were isolated during a planned or elective admission. The exception to this was for planned admissions involving bone marrow or stem cell transplantation. Given the importance of microbial translocation and overgrowth in patients being treated for haematological malignancies [13], we postulated this patient group had underlying *Campylobacter* spp. carriage at the time of admission.

Analysis

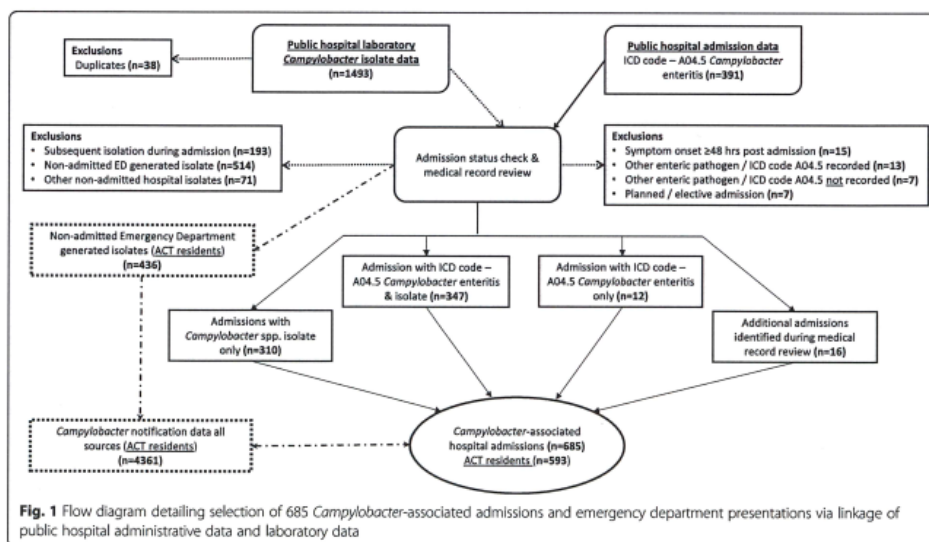
Hospitalisation and non-admitted ED presentation rates were calculated using ACT resident admission and surveillance data. Sensitivity, specificity, positive and negative predictive values for ICD coding using laboratory diagnosis as the gold standard were calculated. Age and gender specific rates of hospitalisation were calculated for ACT residents. Changes in rates and proportions over time were assessed using linear tests for trend, while two-sample tests of proportions were used to assess equality between groups. Relationships between outcome and independent variables were assessed using Pearson's chi-squared or Fisher's exact tests. Equality of median tests and Spearman's correlations were used to analyse non-normally distributed continuous data including age, LOS, CCI score and time to admission.

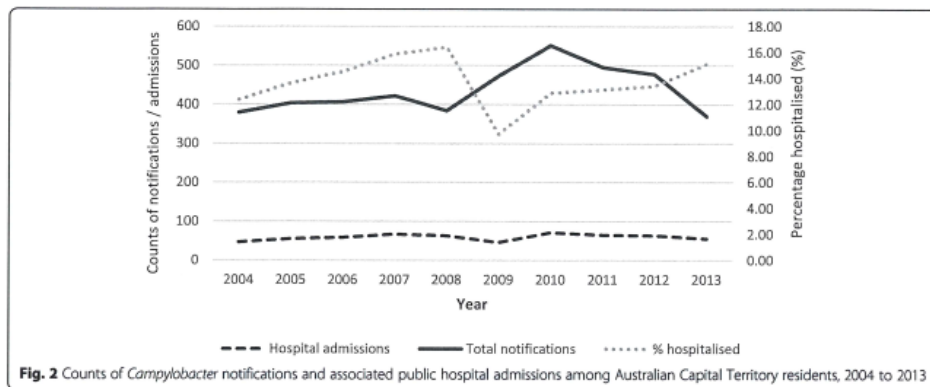
Results

Linking hospital administrative data to laboratory data

We identified 685 *Campylobacter*-associated admissions during the study period (Fig. 1). Hospital administrative data identified 52% (359/685) of admissions, laboratory data 45% (310/685) with the remaining 16 admissions identified via medical record review. For admissions identified via administrative data, 84% (300/359) had *Campylobacter* enteritis recorded as a primary diagnosis code. For admissions identified via laboratory data, primary diagnosis codes were available for 81% (250/310), with two-thirds (168/250) assigned a non-specific gastroenteritis code. Sensitivity of morbidity coding using laboratory diagnosis as the standard was 52.8% (95% CI 48.9–56.7%), and specificity was 57.1% (95% CI 37.2–75.5%). The positive and negative predictive values were 96.7% (95% CI 94.2–98.3%) and 4.9% (95% CI 2.8–7.8%).

ACT residents comprised 86% (593/685) of admissions, with a hospitalisation rate of 13.6% (593/4361) (Fig. 2). EDs were the admission source for 94% (555/593) of ACT resident admissions, with a further 10% (436/4361) of ACT *Campylobacter* notifications linked to at least one non-admitted ED presentation. No trends over time were observed in the proportions of *Campylobacter*-associated admissions or non-admitted ED presentations. Admissions did not appear to show any obvious seasonal pattern (data not shown).





Descriptive characteristics

Age and sex characteristics

Age and sex characteristics are shown in Table 1. Males were older ($M = 41.2$ years, range < 1 to 92.3) than females ($M = 38.5$, range < 1.0 to 92.3) but this difference was not significant. For ACT resident admissions, the median age was 38.4 years (range < 1.0 to 92.3 years), compared with 31 years (range < 1.0 year to 99.0 years) among ACT community cases ($X^2 = 17.7$, $p < 0.001$). Non-ACT residents were significantly older ($M = 50.8$, range < 1 year, maximum 90.8 years, $X^2 = 5.5$, $p = 0.02$). Hospitalisation rates increased noticeably among patients aged ≥ 60 years. The proportion of females admitted across most age-groups was higher than for males, although these differences were small and non-significant (Fig. 3).

Prior care, source of admission and admitting unit

Twenty-seven percent (187/684) of admissions consulted a general practitioner (GP) prior to hospitalisation, while 13.4% (92/685) were hospitalised after an earlier non-admitted ED presentation. There were 29 admissions (4.2%) preceded by both GP consultations and non-admitted ED presentations. EDs were the admission source for 91.8% (629/685) of admissions, with the remainder via community or outpatient admissions, inter-hospital transfers or care type changes.

Length of stay (LOS) The median LOS for *Campylobacter*-associated admissions was 2.0 days (range 1.0–38.0), with no gender or residency differences observed. Exclusion of same day Emergency Medicine unit admissions ($n = 180$), markedly increased the median LOS ($M = 3.0$ days, range 1.0–38.0) and average LOS (Table 1). A moderately positive correlation between age and

LOS was observed (Spearman's $\rho = 0.3557$, $p < 0.001$). Higher median LOS were observed for units including Oncology, Haematology, and Geriatrics, while significant correlations between increasing age and LOS, were observed among General Medicine, Renal Medicine and Gastroenterology admissions (data not shown).

Comorbidities

Comorbidities were documented in 34.6% (237/685) of admissions. The most prevalent were diabetes 30.8% (73/237), malignancies (including solid and disseminated tumours, blood and lymphatic cancers) 27.4% (65/237), chronic kidney disease 19.0% (45/237), cerebrovascular disease 17.3% (41/237) and history of myocardial infarction 13.1% (31/237). The median CCI score was 2 (range 1 to 12). Males comprised 53.6% (127/237) of admissions with comorbidities but no gender differences in CCI score were observed. Admissions with comorbidities were older, having a median age of 66.7 years (range 3.5 to 92.3 years) versus 28.8 years (range < 1.0 to 92.3) ($X^2 = 202.0$, $p < 0.001$). A positive correlation between increasing age and CCI scores was observed ($r_s = 0.18$, $n = 237$, $p < 0.001$). LOS were longer in admissions with comorbidities, with a median of 4.0 days (range 1.00 to 38.0 days) versus 1.0 day (range 1.0 to 22.0, $X^2 = 68.93$, $p < 0.001$). A positive correlation between increasing LOS and CCI scores was demonstrated ($r_s = 0.25$, $n = 237$, $p < 0.001$), while a larger proportion of admissions with comorbidities had times to admission greater than the 3 day median ($X^2 = 4.55$, $p = 0.03$).

Time to admission

The median time between onset and hospitalisation for initial acute admissions ($n = 662$) was 3.0 days (range < 1.0 to 24.0). A higher proportion of females had times to

Table 1 Demographic and clinical characteristics of 685 *Campylobacter*-associated admissions in Australian Capital Territory (ACT) public hospitals, 2004–2013

Gender	
Male (n, %)	350 (51.0)
Female	335 (49.0)
ACT resident (%)	593 (86.6)
Median (M) age in years for all admissions (range)	39.7 (< 1.0–92.3)
Indigenous Australian (%)	7 (1.0)
Age-groups % (hospitalisation rate per 100,000 population ^a)	
0–9 years (n = 30)	4.38 (5.67)
10–19 years (n = 67)	9.78 (11.91)
20–29 years (n = 158)	23.07 (23.72)
30–39 years (n = 93)	13.58 (15.58)
40–49 years (n = 67)	9.78 (11.91)
50–59 years (n = 57)	8.32 (11.17)
60–69 years (n = 68)	9.93 (19.53)
70–79 years (n = 74)	10.80 (39.40)
80+ years (n = 71)	10.36 (65.35)
Acute care admission (%)	673 (98.3)
Average length of stay (range)	
Same day acute admissions (n = 268)	1.0 day
Non-same day acute admissions (n = 405)	4.9 days (2.0–38.0)
Other separation types (n = 12)	8.6 days (1.0–23.0)
Median (M) length of stay (range)	
Non-same day acute admissions (n = 405)	4.0 days (2.0–38.0)
Comorbidity as per Charlson Comorbidity Index (CCI) (count, (percentage))	
CCI score (n, %)	237 (34.5)
1	86 (36.3)
2	81 (34.2)
> 2 (% range)	70 (29.5, 3–12)
Median (M) time to admission from illness onset for acute admissions ^b (range)	3.0 days (< 1.0–23.0)
Key signs of infection ^c	
Electrolyte disturbance (n, %)	410 (60.2)
Tachycardia	241 (35.4)
Renal impairment	127 (18.7)
Hypotension	87 (12.8)
History of recent overseas travel (n, %)	11 (1.6)
Re-admission ≤28 days related to campylobacteriosis, including non-acute status changes (n, %)	38 (5.6)
Intensive care unit admission (n, %)	10 (1.5)
Surgical or invasive diagnostic procedure related to	45 (6.6)

Table 1 Demographic and clinical characteristics of 685 *Campylobacter*-associated admissions in Australian Capital Territory (ACT) public hospitals, 2004–2013 (Continued)

campylobacteriosis (n, %)	
Death during admission or ≤ 28 days post discharge (n, %)	5 (0.7)
Blood sample taken for culture (percentage <i>Campylobacter</i> positive)	333 (7.5)
Antimicrobial therapy during admission (n, %)	219 (32.0)

^aACT residents only ^b636 observations ^c681 observations

admission greater than the median compared to males ($X^2 = 6.03$, $p = 0.01$). A positive correlation between increasing age and time to admission was observed ($r_s = 0.15$, $n = 662$, $p < 0.001$).

Key signs of infection

These were observed in 74.5% (510/685) of admissions (Table 1), with electrolyte imbalance being the most commonly reported. Renal impairment was associated with any CCI-linked comorbidity ($X^2 = 128.30$, $p < 0.001$) along with male gender ($X^2 = 12.56$, $p < 0.001$). Hypotension ($X^2 = 27.91$, $p < 0.001$) and electrolyte imbalances ($X^2 = 22.24$, $p < 0.001$) were also associated with underlying comorbidities. Correlations between the presence of multiple signs of infection (including electrolyte imbalance, tachycardia, renal impairment and hypotension), and increasing age ($r_s = 0.32$, $n = 682$, $p < 0.001$) and LOS ($r_s = 0.22$, $n = 682$, $p < 0.001$) were observed. Admissions without comorbidities were more likely to have bloody diarrhoea, self-reported fevers, abdominal pain and headaches documented, while key signs of infection and *Campylobacter*-associated readmissions occurred more frequently in admissions with comorbidities (Table 2).

Complications and other outcomes

A diversity of complications were documented at discharge, with systemic disease and acute kidney injury the most frequently recorded (Table 3). The median age for admissions with systemic disease was 60.8 years (range 12.0 to 90.1) compared to 38.6 years (range < 1.0 to 92.3) among other *Campylobacter*-associated admissions ($X^2 = 9.60$, $p = 0.002$). The median LOS was 3.5 days (range 1.0 to 28.0), being significantly greater than other admissions ($M = 2.0$ days, range 1.0 to 38.0, $X^2 = 7.70$, $p < 0.01$). An association between comorbidity per se and systemic illness was observed ($X^2 = 8.80$, $p < 0.01$) with individual associations seen for admissions with liver disease ($X^2 = 50.78$, $p < 0.001$) and leukaemia ($X^2 = 5.67$, $p = 0.02$).

Acute Kidney Injury (AKI) was diagnosed among 3.4% (23/685) of admissions. These were significantly older

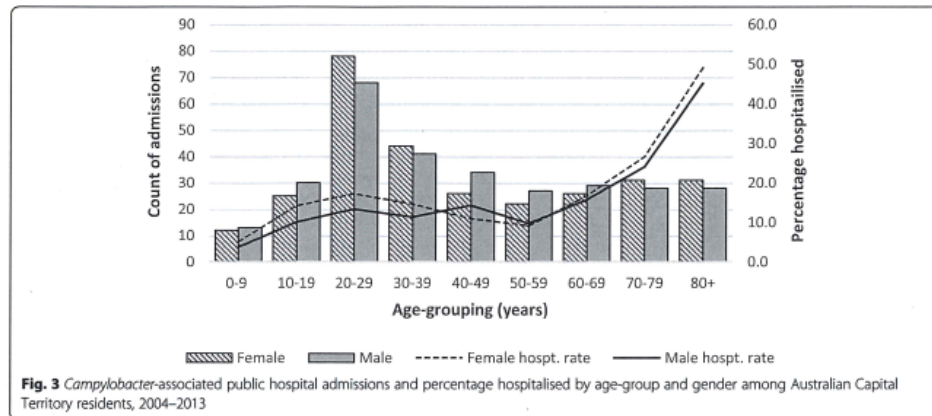


Table 2 Comparison of signs, symptoms, and other outcomes among *Campylobacter*-associated admissions with and without documented comorbidities (as per Charlson Co-morbidity Index)

Signs and symptoms associated with enterocolitis	Comorbidity present (n = 237)				Total	X ²	p-value
	Yes	%	No	%			
Diarrhoea	231	98.7	444	99.1	675	0.23	0.63
Bloody diarrhoea	28	18.7	121	35.2	149	13.51	< 0.001
Self-reported fever	129	58.1	341	78.0	470	28.57	< 0.001
Fever ($\geq 38^{\circ}\text{C}$)	114	50.0	224	51.4	338	0.11	0.74
Abdominal pain	161	81.7	403	95.7	564	33.00	< 0.001
Nausea	142	79.8	311	87.6	453	5.70	0.02
Vomiting	114	58.8	234	56.5	348	0.27	0.60
Myalgia / arthralgia	35	76.1	122	87.1	157	3.22	0.07
Malaise	102	91.9	152	96.8	254	3.18	0.07
Headache	53	66.3	149	89.8	202	20.31	< 0.001
Key signs and symptoms of infection							
Hypotension	52	22.3	35	7.8	87	27.94	< 0.001
Tachycardia	89	38.2	152	33.9	241	1.22	0.27
Electrolyte imbalance	169	72.5	241	53.8	410	22.46	< 0.001
Renal impairment	98	42.1	29	6.5	127	127.95	< 0.001
Acute confusion	34	14.6	4	0.9	38	54.60	< 0.001
Bacteraemia	17	7.2	11	2.5	28	8.80	< 0.01
Other outcomes							
ICU admission	10	4.2	0	–	10		< 0.001 ^a
Death within 28 days of discharge	5	2.1	0	–	5		< 0.01 ^a
<i>Campylobacter</i> -associated readmission	22	9.3	16	3.6	38	9.65	0.002

^a Fisher's exact test

Table 3 Complications recorded at discharge among *Campylobacter*-associated hospital admissions in the Australian Capital Territory, 2004–2013

	Frequency (%)
Extra-intestinal / systemic disease	
Bacteraemia (laboratory proven)	28 (4.1%)
Sepsis (discharge diagnosis)	19 (2.8%)
Intestinal complications	
Appendicitis (histologically confirmed)	8 (1.2%)
Mesenteric adenitis	6 (0.9%)
Acute pancreatitis	4 (0.6%)
Acute cholecystitis	1 (0.2%)
Other significant complication	
Acute kidney injury	23 (3.4%)
Acute myocardial infarction	6 (0.9%)
Delirium	3 (0.4%)
Metabolic acidosis	3 (0.4%)
Atrial fibrillation	2 (0.3%)
Rhabdomyolysis	2 (0.3%)
Febrile seizure	1 (0.2%)
Hypovolemic shock	1 (0.2%)
Spontaneous abortion	1 (0.2%)
Perforated diverticulum	1 (0.2%)
Peritonitis	1 (0.2%)
Pulmonary embolism	1 (0.2%)
Thrombocytopenia	1 (0.2%)
Transient Ischaemic Attack	1 (0.2%)
Reactive complication	
Gillain-Barre Syndrome	2 (0.3%)
Myopericarditis	2 (0.3%)
Reactive arthritis	1 (0.2%)
IgA nephropathy	1 (0.2%)
Unnecessary surgery	
Appendectomy (normal histology)	8 (1.2%)

(M 73.9 years, range 33.2 to 87.5, median test $X^2 = 19.92$, $p < 0.001$), and took longer to present following symptom onset (M 5.0 days, range < 1.0 to 14, $X^2 = 16.87$, $p < 0.001$). No differences in gender, LOS or CCI score were observed among acute admissions without AKI. Renal impairment was observed in 18.7% (123/672) of acute admissions. This group was also older (M 73.8 years, range 23.7 to 92.3, $X^2 = 101.51$, $p < 0.001$), had longer LOS (M 4.0 days, range 1.0 to 31.0, $X^2 = 27.91$, $p < 0.001$), and a greater proportion of admissions with CCI scores > 2 (M 2, range 1 to 12, $X^2 = 29.57$, $p < 0.001$). A significant association with male gender was observed ($X^2 = 12.43$, $p < 0.001$).

Readmissions ≤ 28 days after discharge occurred among 9.6% (66/685) of admissions, with 57.6% (38/66) being *Campylobacter*-associated. These included 27 admissions for ongoing enterocolitis and 11 for non-acute care. The median age and LOS for acute readmissions were 36.9 years (range 10.1 to 85.6) and 1 day (range 1 to 7 days). No gender-based associations were observed.

Surgical or invasive diagnostic procedures ($n = 52$) were performed during 6.6% (45/685) of admissions. Colonoscopies accounted for 46% (24/52), appendectomies 31% (16/52) and gastroscopies 19% (10/52) of procedures. The median age of those undergoing procedures was 28.8 years (range 12.0 to 81.4), significantly lower than for other acute admissions ($M = 40.1$ years, range < 1.0 to 92.3, $X^2 = 8.54$, $p < 0.01$), while median LOS was 4 days (range 1 to 22), being compared to 2 days (range 1 to 38 days, $X^2 = 20.70$, $p < 0.001$).

Discussion

In this study, only one out of every two *Campylobacter* infections was identified via hospital discharge data. While hospitalisation is considered a marker of severity for foodborne bacterial infections [14], estimating enteric pathogen hospitalisations is challenging given concerns regarding the completeness of surveillance data and the accuracy of pathogen-specific diagnoses and morbidity coding [15]. By identifying all hospital-derived *Campylobacter* isolates and linking these to inpatient admissions and surveillance data we calculated the sensitivity of morbidity coding associated with *Campylobacter* infection to be 52%, indicating substantial measurement error. This has been demonstrated in similar settings with US [15] and Swedish [16] studies reporting appropriate use of ICD coding among hospitalised campylobacteriosis cases to be 43 and 51% respectively.

The 14% hospitalisation rate we reported is high, reflecting *Campylobacter*-associated morbidity in Australia [3, 9]. Inter-country comparisons of hospitalisations however reflect differences in incidence and data capture. In New Zealand, 12.6% of cases were reported as hospitalised (although data was complete for only 62.2% of cases) [17] while in Germany, where hospitalisation status is routinely collated, the rate was 10% [18]. Elsewhere hospitalisation rates have ranged from estimates of 5.1% in Canada [19] to 26.9% in a Swedish study [16].

Population characteristics of campylobacteriosis in developed settings are typified by increased disease incidence in males and a bimodal age-distribution, with peaks in children aged < 5 years and adults < 45 years [20]. We observed higher female admission rates across all age groupings, a finding reported in a number of studies examining hospitalisation for enteric infections [21, 22]. Reasons for this remain uncertain but inadequate social support for older women has been

proposed as a contributing factor [21], while our study suggests females may delay seeking care. The increase in admissions aged 20–29 years reflects higher case numbers, with *Campylobacter*-associated hospitalisation rates increasing most dramatically after 60 years. These observations are consistent with reported changes in the population structure for campylobacteriosis in Australia and similar settings [3, 23], highlighting the potential hospitalisation costs for the elderly and necessitating a need for age-specific interventions [24].

Signs and symptoms observed were typical of campylobacteriosis, with most admissions having diarrhoea and abdominal pain recorded [4]. Reports suggest older campylobacteriosis cases may report some signs and symptoms, including bloody diarrhoea, abdominal pain, vomiting and fevers less frequently [25]. Our data support this juxtaposition, although it seems unlikely that age-related differences in presentation would impact a *Campylobacter* diagnosis due to the proclivity of stool testing.

Reported LOS vary dependent upon the measures of central tendency used. We reported mean and median LOS of 3.5 and 2.0 days, while for acute non-same day admissions the mean and median LOS were 4.9 and 4.0 days. These appear comparable to findings elsewhere [19, 26]. Similarly we observed cases with bacteraemia or underlying comorbidities to have longer LOS [27, 28]. Notably 40% of admissions involved same day care, illustrating the spectrum of hospitalisation, while linkage of surveillance and laboratory data revealed 10% of non-hospitalised cases presented to EDs for non-admitted acute care. Reasons for this ED burden might include perceived symptom severity and lack of access to a GP [29].

One third of patients had a comorbidity, a proportion similar to studies describing hospitalisations for infectious gastroenteritis [27]. These patients were generally older, took longer to present and had longer LOS. Diabetes was the most frequently recorded comorbidity, followed by malignancies and chronic kidney disease. While some evidence suggest diabetes and chronic kidney disease increase risk for *Campylobacter* enterocolitis [30, 31], relationships between *Campylobacter* infection and malignancies are more well established [32, 33]. Admissions with comorbidities experienced electrolyte imbalances, renal impairment, hypotension, acute confusion and acute readmission more frequently.

Half of acute admissions had blood cultures, with a positivity rate of 7.5%. These admissions involved older patients with higher comorbidity levels, although associated mortality was low, features consistent with findings elsewhere [28, 34]. Although no deaths occurred among blood culture positive cases, there was one death in a case diagnosed with blood culture negative sepsis.

Our study suggests renal impairment may occur more frequently in patients' hospitalised with campylobacteriosis.

This is supported by studies describing increased renal dysfunction among hospitalised gastroenteritis cases [30, 35, 36]. Furthermore comorbidities including kidney disease, hypertension, diabetes and a history of organ transplantation have been shown to increase AKI risk among patients with infectious diarrhoea [30].

Around 7% of admissions underwent surgical or invasive diagnostic procedures, with appendectomies and colonoscopies most frequently performed. Among appendix specimens, 50% showed histological evidence of inflammation, although specimens were not microbiologically tested. The issue of *Campylobacter*-associated appendicitis remains contentious, with a study re-examining archived appendices using nucleic acid testing detecting *C. jejuni* in 22% of specimens [37].

Limitations with our study include the cross-sectional design and generalisability of findings given the small provincial source population [38]. Local epidemiology is also an important consideration, with ACT campylobacteriosis rates higher than most other Australian states [3]. Differences in health care utilisation also require consideration [39]. We assumed hospitalisation would most likely occur in the public sector, with the extent of private hospital admissions being uncertain. Given the size and role of private hospitals in Australia's health care system [40], our calculated rate of hospitalisation for ACT residents may be an underestimation. We were unable to estimate predictors of hospitalisation, however access to integrated Australian hospital and primary care data is lacking [41], making comparisons challenging. While plausible, our findings regarding AKI and renal impairment require further assessment. AKI diagnoses were not validated against a standard, e.g. Kidney Disease: Improving Global Outcomes (KDIGO) criteria [42], while our assessment of renal impairment via serum creatinine levels was simplified.

Conclusion

Hospitalisation data provides an important indicator of the burden and severity of campylobacteriosis. Improving the accuracy and completeness of *Campylobacter*-associated hospitalisation data, in conjunction with detailed clinico-epidemiological characterisation is of tangible benefit to clinicians and public health decision makers. Undertaking observational studies, including genomic assessment of virulence factors, would improve understanding of patient and pathogen specific predictors of hospitalisation.

Abbreviations

ACT: Australian Capital Territory; AKI: Acute Kidney Injury; CCI: Charlson Comorbidity Index; ED: Emergency Department; GP: General Practitioner; ICD: International Classification of Diseases; LOS: Length of Stay; NSW: New South Wales; UR: Unit Record; US: United States

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Authors' contributions

CM planned the study, undertook data collection, performed analysis and drafted the manuscript. CM, KK, LS and MK all contributed to and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the ACT Government Health Directorate and Calvary Health Care (Bruce). Restrictions apply to the availability of these data, which were used under approvals for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ACT Government Health Directorate and Calvary Health Care (Bruce).

Ethics approval and consent to participate

Ethics approvals were obtained from the Human Research Ethics Committee of the ACT Government Health Directorate (Ref. ETHLR.14.121) Calvary Health Care (Bruce) (Ref. 22–2014) and the Australian National University (Ref. 2014/223). These approvals included permission to access inpatient medical records subject to the study dataset being anonymised before use. Individual consent to participate was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

Author details

¹National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, ACT 2602, Australia. ²Department of Microbiology, Canberra Hospital and Health Services, Canberra, ACT, Australia. ³School of Public Health, University of Queensland, Brisbane, QLD, Australia.

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RESEARCH ARTICLE

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Bacteraemia, antimicrobial susceptibility and treatment among *Campylobacter*-associated hospitalisations in the Australian Capital Territory: a review

Cameron R. M. Moffatt^{1*}, Karina J. Kennedy², Ben O'Neill¹, Linda Selvey³ and Martyn D. Kirk¹

Abstract

Background: *Campylobacter* spp. cause mostly self-limiting enterocolitis, although a significant proportion of cases require hospitalisation highlighting potential for severe disease. Among people admitted, blood culture specimens are frequently collected and antibiotic treatment is initiated. We sought to understand clinical and host factors associated with bacteraemia, antibiotic treatment and isolate non-susceptibility among *Campylobacter*-associated hospitalisations.

Methods: Using linked hospital microbiology and administrative data we identified and reviewed *Campylobacter*-associated hospitalisations between 2004 and 2013. We calculated population-level incidence for *Campylobacter* bacteraemia and used logistic regression to examine factors associated with bacteraemia, antibiotic treatment and isolate non-susceptibility among *Campylobacter*-associated hospitalisations.

Results: Among 685 *Campylobacter*-associated hospitalisations, we identified 25 admissions for bacteraemia, an estimated incidence of 0.71 cases per 100,000 population per year. Around half of hospitalisations (333/685) had blood culturing performed. Factors associated with bacteraemia included underlying liver disease (aOR 48.89, 95% CI 7.03–340.22, $p < 0.001$), Haematology unit admission (aOR 14.67, 95% CI 2.99–72.07, $p = 0.001$) and age 70–79 years (aOR 4.93, 95% CI 1.57–15.49). Approximately one-third (219/685) of admissions received antibiotics with treatment rates increasing significantly over time ($p < 0.05$). Factors associated with antibiotic treatment included Gastroenterology unit admission (aOR 3.75, 95% CI 1.95–7.20, $p < 0.001$), having blood cultures taken (aOR 2.76, 95% CI 1.79–4.26, $p < 0.001$) and age 40–49 years (aOR 2.34, 95% CI 1.14–4.79, $p = 0.02$). Non-susceptibility of isolates to standard antimicrobials increased significantly over time ($p = 0.01$) and was associated with overseas travel (aOR 11.80 95% CI 3.18–43.83, $p < 0.001$) and negatively associated with tachycardia (aOR 0.48, 95%CI 0.26–0.88, $p = 0.02$), suggesting a healthy traveller effect.

*Correspondence: cameron.moffatt@anu.edu.au

¹ National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, 2602 Canberra, ACT, Australia

Full list of author information is available at the end of the article



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Conclusions: *Campylobacter* infections result in considerable hospital burden. Among those admitted to hospital, an interplay of factors involving clinical presentation, presence of underlying comorbidities, complications and increasing age influence how a case is investigated and managed.

Keywords: *Campylobacter* infections, Hospitalisation, Bacteraemia, Incidence, Antimicrobial susceptibility, Antimicrobial therapy, Comorbidity, Elderly

Background

Campylobacter spp. are internationally significant as a cause of infectious diarrhoeal disease [1]. Most cases of infectious diarrhoea, including those caused by *Campylobacter* spp., are self-limiting, with management focused on maintenance of hydration via fluid repletion [2]. However, for persons hospitalised with *Campylobacter* infection, clinical thresholds for exclusion of bacteraemia and the consideration of antimicrobial therapy differ due to symptom severity, risk of complications or the exacerbation of underlying co-morbidities [2].

While bacteraemia is an uncommon complication of campylobacteriosis, testing and diagnosis typically occurs when a person is hospitalised [3]. Within a hospital setting, clinical tolerances and the challenge of predicting bacteraemia among febrile admissions with an enteric focus are important considerations [4]. Further, the likelihood of clinicians commencing antibiotic therapy may also increase among hospitalised cases, highlighting the importance of judicious prescribing and understanding of isolate susceptibility patterns to ensure viable treatment options remain [5].

We describe rates of bacteraemia, antimicrobial susceptibility and treatment among a cohort of *Campylobacter*-associated hospitalisations. We also examined clinical and host factors associated with the diagnosis of blood stream infections (BSI), isolate non-susceptibility and antibiotic treatment of hospitalised cases.

Methods

Background and data

This study forms part of a retrospective review of *Campylobacter*-associated hospital admissions in the Australian Capital Territory (ACT) between January 2004 and December 2013. A *Campylobacter*-associated hospital admission was defined as any episode of care for an admitted patient that was clinically and temporally linked to a *Campylobacter* isolate derived from the same patient. Full details of the setting, data sources, data collection and linkage are described elsewhere [6]. In summary, they include hospital generated admission data, hospital microbiology data and clinical data obtained via individual medical record review. Hospital admission details were obtained via a data extract that included patient demographics, admission and discharge dates and

admission unit details. Record inclusion was determined by an inpatient admission having been assigned an International Classification of Diseases (ICD) diagnosis code 'A045—*Campylobacter* enteritis'. We also obtained a separate microbiology data extract detailing inpatient isolations of *Campylobacter* spp., including specimen type, collection dates and antimicrobial susceptibility data. All laboratory diagnoses of *Campylobacter* infection were made via culture; speciation was not routinely performed on hospital isolates prior to 2013. Susceptibilities to ciprofloxacin, nalidixic acid and erythromycin were assessed using disk diffusion and according to Clinical and Laboratory Standards Institute breakpoints [7]. Intermediate and resistant isolates were grouped as non-susceptible to aid analysis. Due to the potential for multiple specimens being collected during an individual admission (or across multiple related admissions), we reported antimicrobial susceptibility using the earliest available data. Microbiology results were then linked to both admissions with and without ICD code 'A045'. We undertook a review of medical records to collect additional details on illness presentation, associated complications, patient co-morbidities (as per the Charlson Co-morbidity Index) [8] and antibiotic treatment and prescribing details (e.g., antibiotic type, dosage, frequency and administration route). For antibiotic treatment, we defined a total daily dose as the dosage in milligrams (mg) multiplied by the frequency of administration per day, with the product expressed in milligrams per day.

Statistical analysis

We calculated bacteraemia incidence per 100,000 persons using the ACT's mid-year estimated resident population for each year between 2004 and 2013 [9]. We used non-parametric methods, including median tests, to analyse non-normally distributed variables such as age. We used Pearson's chi-squared test and Fisher's exact tests to assess simple statistical associations between key outcome and independent variables of interest, while trends in proportions were assessed using chi-squared tests. Preliminary analyses included the estimation of relative risks (RRs), 95% confidence intervals (CIs) and p-values to assess potential predictors of blood culturing, antimicrobial susceptibility and antibiotic treatment. Variables examined included age, sex, country of birth, previous

Campylobacter-associated hospitalisation, overseas travel history, signs and symptoms, admission unit, comorbidities and the presence of key signs of infection. Using a stepwise additive approach, with the most significant variables being added first, we constructed separate logistic regression models to identify predictors associated with (i) collection of blood specimens for culture, (ii) positive blood isolates, (iii) non-susceptibility to ciprofloxacin, (iv) any antimicrobial non-susceptibility and (vii) antibiotic treatment during hospitalisation. Erythromycin non-susceptibility was not assessed due to the limited number of observations. Clinical relevance and statistical evidence were used to assist with variable selection for multivariable analysis. The significance level for removal from the models was set at $p \leq 0.05$. We used likelihood-ratio tests to assess the explanatory power of the models, with the variable expressing the largest p -value being removed. Final results were expressed as adjusted odds ratios (aOR), with accompanying 95% confidence intervals and p -values. We used Hosmer-Lemeshow tests to assess the goodness-of-fit for each model. All statistical analyses were performed using Stata v.14 (StataCorp, USA).

Results

Campylobacter bacteraemia

Out of 685 admissions, 333 (49%) had blood drawn for culture and 25 (7.5%) of these tested positive (Fig. 1). Speciation was performed on 21 (84%) of these case isolates with 15 (71.4%) cases of *C. jejuni*, 5 (23.8%) cases of *C. coli* and a single (4.0%) case of *C. lari* bacteraemia. Amongst the 25 admissions with bacteraemia, 15 were male (60%) and 10 were female (40%), while the median age was 59.5 years (range 12 to 90 years). Amongst 308 negative cases there were 177 males (57.5%) and 131 females (42.5%), with a median age of 38.8 years (age range < 1.0 to 92 years). This age difference was significant (median test $\chi^2 = 5.30$, $p = 0.02$) but no evidence of a difference in the sex composition was observed ($\chi^2 = 0.06$, $p = 0.81$). The age and sex of admissions in relation to blood culture status is shown in Fig. 2. We also compared those who had blood drawn for culture (whether positive or negative) with those that did not to assess demographic differences. We saw no evidence of a difference in median age (median test $\chi^2 = 0.18$, $p = 0.68$) but did observe males to be more likely to have blood drawn ($\chi^2 = 11.17$, $p = 0.001$). We observed no difference in the proportion of admissions with documented comorbidities who had blood specimens collected for culture when compared to admission without comorbidities who had blood taken for culture ($\chi^2 = 1.42$, $p = 0.23$). Bacteraemia generally occurred in the context of antecedent diarrhoeal illness,

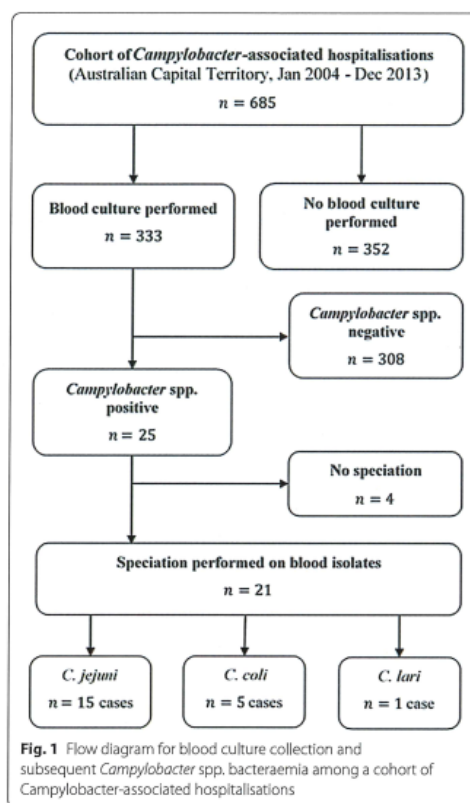
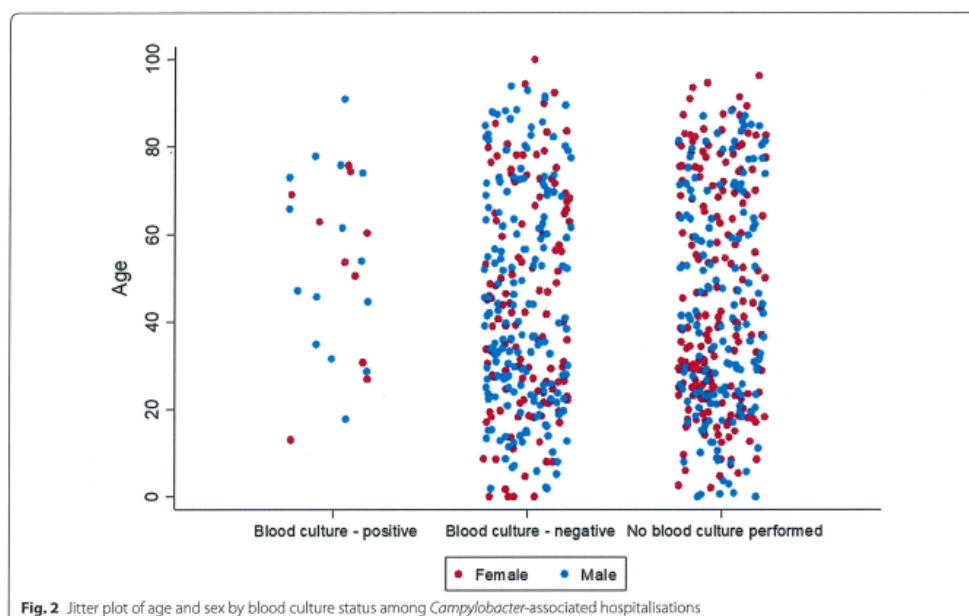


Fig. 1 Flow diagram for blood culture collection and subsequent *Campylobacter* spp. bacteraemia among a cohort of *Campylobacter*-associated hospitalisations

although two admissions involved primary bacteraemia (i.e. without diarrhoea) in patients with haematological malignancies. Comorbidities, while common, were not a characteristic feature of cases hospitalised with bacteraemia as shown in Table 1. No deaths were identified among cases with bacteraemia.

During the period 2004 to 2013, the mean incidence of *Campylobacter* bacteraemia in the host population was 0.71 cases per 100,000 population per year (95% CI 0.48–1.05 per 100,000 population) (Fig. 3). We did not observe temporal trends in the proportion of *Campylobacter*-associated hospitalisations undergoing blood collection for culture or in the proportion of positive blood cultures among *Campylobacter*-associated hospitalisations.

Factors associated with the collection of blood samples for culture and subsequent isolation of *Campylobacter* spp. are shown in Tables 2 and 3.



Antimicrobial susceptibility

We identified 548 *Campylobacter*-associated admissions with a primary isolation of *Campylobacter* spp. and where subsequent antimicrobial susceptibility testing was performed. For 526 (96%) of these cases there was available data for three standard antimicrobials, ciprofloxacin, nalidixic acid and erythromycin. Of the remainder, nalidixic acid data was unavailable for 21 isolates, with erythromycin susceptibility unavailable for a single isolate.

During the study period, 13% (70/548) of primary isolates exhibited non-susceptibility to at least one standard antimicrobial. The proportion of non-susceptible isolates ranged from $\leq 5.0\%$ in 2004/05 to $>20.0\%$ in 2012/13, with this increase being significant ($\chi^2 = 6.12$, $p = 0.01$) (Fig. 4). Among the individual antimicrobials, nalidixic acid non-susceptibility was reported for 9% (49/527) of tested isolates, 7% (40/548) for ciprofloxacin and 4% (21/547) for erythromycin.

Figure 4 shows that lower rates of erythromycin non-susceptibility were observed while significant increases in both ciprofloxacin ($\chi^2 = 16.51$, $p < 0.001$) and nalidixic acid non-susceptibility occurred during the study period ($\chi^2 = 10.85$, $p = 0.001$). Factors associated with antimicrobial non-susceptibility among *Campylobacter*-associated hospitalisations are shown in Tables 4 and 5.

Antibiotic treatment

Antimicrobial treatment was provided for 32% (219/685) of *Campylobacter*-associated hospitalisations. Those receiving treatment were observed to be significantly older (median 48.5 years, range 8 years to 92 years) than admissions where antibiotics were not administered (median 34.8 years, range < 1 years to 91 years, $\chi^2 = 26.92$, $p < 0.001$). No sex-based differences were observed. Treatment associated with bacteraemia is described in Table 1.

Second generation fluoroquinolones were used in 79% (172/219) of treated admissions. Ciprofloxacin was administered to 82.0% (141/172), with the remainder receiving norfloxacin. Those receiving ciprofloxacin were younger (median 47.2 years, minimum 12 years, maximum 90 years) compared with those receiving norfloxacin (median age 64.3 years, minimum 19 years to maximum 92 years), but this difference was not significant. For admissions treated with ciprofloxacin, 91.4% (129/141) received treatment orally, with a median total daily dose of 1000 mg. For those receiving parenteral ciprofloxacin ($n = 12$), the median total daily dose was 800 mg. The median total daily dosage for oral norfloxacin ($n = 31$) was 800 mg.

Macrolides (azithromycin or erythromycin) were administered to 21.0% (46/219) of admissions, with

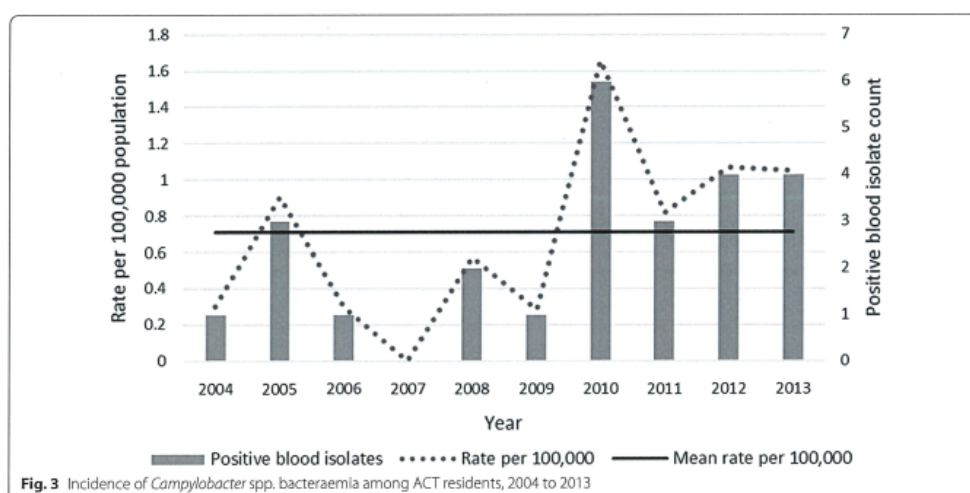
Table 1 Characteristics of cases hospitalised with *Campylobacter* bacteraemia, 2004 to 2013

Year (case)	Age range/sex	Species	Bacteraemia—source	Antimicrobial susceptibility	Antimicrobial treatment	Significant medical history and risk factors
2004	80+ M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	Nil	Age, nil other significant
2005 (a)	50–59 F	<i>Campylobacter</i> sp.	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	Acute myeloid leukaemia
2005 (b)	60–69 F	<i>Campylobacter</i> sp.	Enteric—secondary	Fully sensitive	Nil	Nil significant
2005 (c)	40–49 F	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	IV drug use, PUD on omeprazole
2006 (a)	40–49 M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	Untreated Stage III HIV
2008 (a)	20–29 M	<i>Campylobacter</i> sp.	Enteric—secondary	Fully sensitive	IV azithromycin 500 mg qd	Nil significant
2008 (b)	60–69 M	<i>C. coli</i>	Primary bacteraemia	Ciprofloxacin-Resistant Erythromycin-Resistant	Nil	Lymphocytic lymphoma
2009	30–39 F	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 250 mg bd	History of renal transplant secondary to IgA nephropathy
2010 (a)	60–69 M	<i>Campylobacter</i> sp.	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	Bowel carcinoma, current chemotherapy
2010 (b)	30–39 M	<i>C. coli</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	Alcoholic liver disease with portal hypotension and bleeding varices
2010 (c)	70–79 F	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	T2DM
2010 (d)	10–19 F	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO azithromycin 500 mg qd (upon discharge)	Nil significant.
2010 (e)	70–79 F	<i>C. coli</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	T2DM
2010 (f)	40–49 M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO Norfloxacin 400 mg bd	Irritable bowel syndrome
2011 (a)	60–69 M	<i>C. lari</i>	Enteric—secondary	Ciprofloxacin—Resistant	PO Doxycycline 100 mg bd	Alcoholic liver disease with portal hypotension, recent intracerebral bleed
2011 (b)	80+ M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	Nil prescribed	Age, nil other significant
2011 (c)	70–79 M	<i>C. coli</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	Asplenic
2012 (a)	40–49 M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	IV ciprofloxacin 500 mg bd	Multiple sclerosis, current chemotherapy pre-stem cell transplantation, IDDM
2012 (b)	30–39 F	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	Nil	Pregnant 33/40K, IDDM
2012 (c)	70–79 M	<i>C. jejuni</i>	Enteric—secondary	Ciprofloxacin—Resistant Nalidixic acid—Resistant	Nil	Diabetic neuropathy, chronic renal failure
2012 (d)	60–69 F	<i>C. coli</i>	Enteric—secondary	Ciprofloxacin—Resistant Nalidixic acid—Resistant	Nil	Nil significant
2013 (a)	20–29 M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	Nil	Nil significant
2013 (b)	20–29 M	<i>C. jejuni</i>	Primary bacteraemia	Fully sensitive	PO Ciprofloxacin 750 mg bd (upon discharge)	B cell leukaemia, AVN (on steroids), SIADH

Table 1 (continued)

Year (case)	Age range/sex	Species	Bacteraemia—source	Antimicrobial susceptibility	Antimicrobial treatment	Significant medical history and risk factors
2013 (c)	50–59 M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	PO ciprofloxacin 500 mg bd	Liver failure with cirrhosis, portal hypotension secondary to Hepatitis C, T2DM, hypothyroidism. Awaiting transplant.
2013 (d)	70–79 M	<i>C. jejuni</i>	Enteric—secondary	Fully sensitive	Nil	Age, nil other significant

PO, per oral; IV, intravenous; PUD, peptic ulcer disease; HIV, human immunodeficiency virus; T2DM, type 2 diabetes mellitus; IDDM, insulin dependent diabetes mellitus; AVN, acute vascular necrosis; SIADH, syndrome of inappropriate antidiuretic hormone

**Fig. 3** Incidence of *Campylobacter* spp. bacteraemia among ACT residents, 2004 to 2013**Table 2** Factors associated with collection of blood for culture among a cohort of *Campylobacter*-associated hospitalisations ($n = 663$)

Predictor variable	Estimated adjusted Odds Ratio (aOR)	95% Confidence interval	p-value
Infectious Diseases Unit admission	8.00	1.58–40.61	0.01
Febrile during admission ($\geq 38^\circ\text{C}$)	21.30	13.76–32.96	<0.001
Tachycardia	1.75	1.13–2.72	0.01
Moderate to severe renal disease	2.87	1.26–6.55	0.01
10–19 years age group	0.36	0.19–0.71	<0.01

22 observations contained missing data

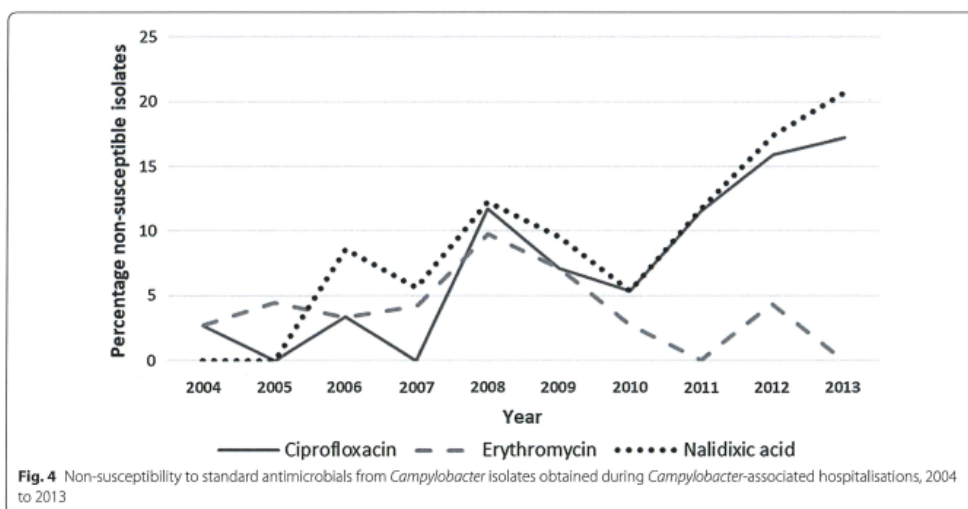
Hosmer and Lemeshow goodness of fit $\chi^2 = 2.70$, $p = 0.61$

63.0% (29/46) receiving azithromycin. No age or sex differences were observed between those receiving azithromycin versus erythromycin. For admissions receiving azithromycin, 72.4% (21/29) received treatment orally, with a median total daily dose for both oral and IV azithromycin of 500 mg. Oral administration was provided for 94.1% (16/17) of admissions

receiving erythromycin, with a median total daily dose of 2000 mg. One patient received an initial total daily dose of 3200 mg IV erythromycin, prior to this being reduced to a total daily dose of 1600 mg. For two admissions (involving the same patient), a tetracycline (doxycycline) was used to treat a *C. lari* bacteraemia and enterocolitis.

Table 3 Factors associated with blood stream isolation of *Campylobacter* spp. among *Campylobacter*-associated hospitalisations ($n = 333$)

Predictor variable	Estimated adjusted Odds Ratio (aOR)	95 % Confidence interval	p-value
Moderate to severe liver disease	48.89	7.03–340.22	< 0.001
Haematology Unit admission	14.67	2.99–72.07	0.001
Age group 70–79 years	4.93	1.57–15.49	< 0.01
Admission during summer months	2.93	1.14–7.57	0.03
Indigenous Australian	10.87	1.00–117.89	0.05

Hosmer and Lemeshow goodness of fit $\chi^2 = 0.71$, $p = 0.70$ **Table 4** Factors associated with ciprofloxacin non-susceptible isolates among *Campylobacter*-associated hospitalisations ($n = 411$)

Predictor variable	Estimated adjusted Odds Ratio (aOR)	95 % Confidence interval	p-value
Bloody diarrhoea	0.30	0.09–1.03	0.06
Recent overseas travel	15.53	2.86–84.18	0.001
Previous <i>Campylobacter</i> -associated hospitalisation	12.87	1.72–96.12	0.01

Hosmer and Lemeshow goodness of fit $\chi^2 = 0.03$, $p = 0.86$ **Table 5** Factors associated with non-susceptibility to ciprofloxacin, nalidixic acid or erythromycin among a cohort of *Campylobacter*-associated hospitalisations ($n = 548$)

Predictor variable	Estimated adjusted Odds Ratio (aOR)	95 % Confidence interval	p-value
Recent overseas travel	11.80	3.18–43.83	< 0.001
Previous <i>Campylobacter</i> -associated hospitalisation	17.09	2.65–110.07	< 0.01
Tachycardia	0.48	0.26–0.89	0.02

Hosmer and Lemeshow goodness of fit $\chi^2 = 0.01$, $p = 0.92$

A significant increase in the proportion of *Campylobacter*-associated hospitalisations being administered antimicrobials was observed over time ($\chi^2 = 4.37$, $p = 0.04$), rising from 27% (14/52) in 2004 to 38% (26/68)

of admissions in 2013. No difference in the proportion of admissions treated with either fluoroquinolones or macrolides was observed. Among admissions receiving macrolides a significant increase in the administration

of azithromycin over erythromycin was observed ($\chi^2 = 16.31$, $p < 0.001$), most notably from 2011 onwards. No changes over time in the proportion of admissions treated with ciprofloxacin versus norfloxacin were observed. Factors associated with administration of antibiotics during *Campylobacter*-associated hospitalisations are shown in Table 6.

Discussion

We observed a high rate of bacteraemia in this study of *Campylobacter*-associated hospital admissions. Although blood cultures are not routinely performed for cases admitted with infectious gastroenteritis, we observed for *Campylobacter*-associated hospitalisations the presence of fever, pre-existing kidney disease or admission to particular subspecialty units increased the likelihood of blood being collected. Comorbidity and advanced age were both associated with a subsequent isolation from blood. One third of admissions received antibiotic treatment during the study period, with the proportion of those treated rising significantly over time. We also observed a temporal increase in the proportion of isolates exhibiting non-susceptibility to standard antimicrobials, notably fluoroquinolones. This is notable given the clinical and public health concern about development of antimicrobial resistance. Factors associated with ciprofloxacin resistance included recent overseas travel and previous hospitalisation for campylobacteriosis. This carries important clinical consequences, as the option to treat with antibiotics may carry greater importance

among hospitalised cases compared to non-hospitalised cases.

Campylobacteriosis most commonly presents as a self-limiting enterocolitis, with secondary bacteraemia a recognised, but relatively infrequent complication [10]. A number of studies have sought to determine the incidence of *Campylobacter* bacteraemia in high-income settings, estimating rates to be between 0.20 and 0.47 cases per 100,000 population [3, 11, 12]. A more recent Swedish study [13] has reported an incidence of 1.00 case per 100,000 population, with this linked to changes in automated blood culture collection systems. In our study we observed only 25 incident cases of bacteraemia, equating to a mean incidence of 0.71 cases per 100,000 population. While bacteraemia is relatively infrequent, our population rates appears high, likely reflecting high background incidence of campylobacteriosis in the ACT [14] and a lower threshold for testing among hospitalised cases.

Blood cultures are the gold standard for the diagnosis of BSIs [4]. In our study, patients who had a measured fever ($\geq 38^\circ\text{C}$), underlying chronic kidney disease or who were admitted under the care of the Infectious Diseases Unit were more likely to have blood drawn for culture. Fever is a common prompt for blood cultures, with patients whose measured temperatures are $\geq 38^\circ\text{C}$ having increased likelihood of bacteraemia [15]. Similarly tachycardia, another vital sign, has also been used in clinical prediction rules for blood-stream infection [16]. Although comorbidities do not feature in BSI underlying kidney disease has also been shown as a risk factor for bloodstream infections in older patients [17]. Several consequences of kidney disease have been proposed to contribute to infection including malnutrition, chronic inflammation, retained uremic solutes, trace element deficiencies and metabolic abnormalities [18]. The finding that blood culture is more likely to be ordered by Infectious Diseases clinicians is unsurprising given the clinical focus of this subspecialty. Conversely, there was significant evidence that those aged between 10 and 19 years were less likely to have blood cultures performed. This finding likely reflects fewer hospitalisations being observed due to the low incidence of campylobacteriosis in this age grouping [14].

Predicting BSIs is challenging with numerous models developed for specific populations, settings and sources of infection [19]. The pre-test probability of bacteraemia will therefore vary considerably based upon the clinical context and source of infection [15]. Generally only 5–10% of blood cultures are positive, and of those positive results, between 30 and 50% represent contaminants [19]. In our study we observed blood cultures to be routinely requested, with 49% of acute admissions having blood drawn and 7% being positive for *Campylobacter*

Table 6 Factors associated with antibiotic administration among a cohort of *Campylobacter*-associated hospitalisations ($n = 607$)

Predictor variable	Estimated adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
Age 0–9 years	0.07	0.01–0.57	0.01
Age 10–19 years	0.44	0.20–0.97	0.04
Age 40–49 years	2.34	1.14–4.79	0.02
Emergency Unit admission	0.06	0.02–0.17	< 0.001
Gastroenterology admission	3.75	1.95–7.20	< 0.001
Gen. Medicine admission	2.02	1.22–3.35	< 0.01
Infectious Diseases admission	2.58	1.03–6.44	0.04
Vomiting	1.70	1.11–2.61	0.02
Electrolyte imbalance	1.73	1.12–2.67	0.01
Blood specimen for culture	2.76	1.79–4.26	< 0.001

Hosmer and Lemeshow goodness of fit χ^2 9.23, $p = 0.32$

spp. These admissions involved both immunosuppressed and immunocompetent patients. The impacts of comorbid and immunosuppressive conditions on clinical variables used in predicting bacteraemia is less well understood [15], although associations with campylobacteriosis and invasive disease in immunosuppressed patients have been described [3, 20]. Transient bacteraemia may also be common among immunocompetent hosts with *Campylobacter* enterocolitis but is less frequently detected due to the bactericidal effect of human serum and reduced frequency of blood culture among acute enterocolitis patients [10], although nearly half of acute admissions in our study had blood culturing performed. Notably, similar proportions of acute admissions with and without comorbidities were observed to have blood drawn for culture suggesting in our study population that comorbidity exerted limited influence on decisions to request blood cultures. This is perhaps not surprising given prediction rules for BSI focus on clinical signs [15].

Factors associated with a positive blood stream isolate (bacteraemia)

The statistical association we observed between cases with positive blood cultures and the presence of underlying liver disease and haematological malignancy is in keeping with hospital-based studies showing higher proportions of these conditions among cases with *Campylobacter* bacteraemia [11, 21, 22]. In addition, advanced age was also statistically associated with detection of bacteraemia, a characteristic seen in larger population-based studies of campylobacteriosis [3]. Several studies also report seasonality with *Campylobacter* bacteraemia [23, 24]. Our results show hospitalisation during the southern hemisphere summer to be associated with bacteraemia, a finding that aligns with the seasonality of *Campylobacter* enteritis in Australia [14]. A further association with blood culture positivity was Indigenous status. This result was derived however from a small number of observations with, Indigenous Australians comprising 1% of *Campylobacter*-associated hospitalisations in the ACT [6].

Factors associated with non-susceptibility to antimicrobials

We observed statistically significant evidence of an increase in the proportion of isolates exhibiting non-susceptibility to standard antimicrobials, with this increase driven primarily by non-susceptibility to fluoroquinolones (including nalidixic acid). In keeping with trends in comparable settings only low rates of non-susceptibility to macrolides were observed [25, 26]. Internationally, fluoroquinolone resistance among *Campylobacter* spp.

has become a major public health problem [5]. Increases in the proportion of clinical isolates demonstrating ciprofloxacin resistance has been observed in the United Kingdom (UK) and United States (US) [25, 27], while in the European Union (EU) more than half (54.6%) of human-associated *C. jejuni* and two-thirds (66.6%) of *C. coli* isolates were resistant to ciprofloxacin in 2013 [28].

Australia has previously reported low rates of fluoroquinolone non-susceptibility among clinical *Campylobacter* isolates (around 2% in 2006) [29]. This has been credited to a national pharmaceutical subsidy scheme that restricted human quinolone use and through regulation forbidding quinolone use in food-producing animals [30]. More recent studies reveal this situation has changed markedly, with current rates of ciprofloxacin resistance in clinically-derived *Campylobacter* isolates now ranging between 13 and 20% [31, 32].

Overseas travel is a well-established risk factor for the acquisition of ciprofloxacin-resistant *Campylobacter* infections [26, 33]. In our study, cases with ciprofloxacin resistance all reported travel to India and South-East Asia, destinations associated with high rates of antimicrobial resistance among enteric pathogens (including *Campylobacter* spp.) [34, 35]. Nevertheless, the majority of ciprofloxacin non-susceptible isolates in our study had no recent overseas travel identified, meaning factors associated with domestic acquisition of ciprofloxacin resistance require greater consideration. US data similarly shows increases in domestically acquired ciprofloxacin resistance [27].

We observed that ciprofloxacin non-susceptibility was also associated with previous hospitalisation with campylobacteriosis. There is a paucity of population-level data on recurrent hospitalisations involving non-susceptible *Campylobacter* isolates. However, rates of recurrent campylobacteriosis in community settings have been reported to be as high as 248 episodes per 100,000 cases per year in the five years following an initial infection [36]. Explanations for our finding could be either host or pathogen-related, including higher rates of humoral immunodeficiency in patients hospitalised with recurrent campylobacteriosis [11, 37] or because of *de novo* mutations or increases in resistant organisms already present at subclinical levels.

While there has been debate around isolate non-susceptibility and disease severity, reanalysis of the issue appears to show no substantial clinical differences between resistant and susceptible *Campylobacter* isolates [38]. Consequently, our finding of reduced odds for bloody diarrhoea and tachycardia among admissions with ciprofloxacin non-susceptibility and any antimicrobial non-susceptibility respectively, most likely represents the so-called “healthy traveller” effect [39].

Factors associated with antibiotic treatment during admission

During the study period we observed statistically significant evidence of an increase in the proportion of *Campylobacter*-associated hospitalisations receiving antibiotic treatment. Antimicrobial therapy for *Campylobacter* enterocolitis is not routinely advised but may be recommended for patients with or at risk of severe disease, including high volume or bloody diarrhoea, high fever, symptom duration greater than one week, pregnancy or immunocompromised status [2, 10, 40]. Given that hospitalisation can be viewed as a marker of disease severity [41], the rates of treatment within our study population might be expected to differ from those among non-hospitalised campylobacteriosis cases.

Other research on campylobacteriosis in the ACT has found no concomitant increase in hospitalisations during the same period as the current study [6]. Antibiotic treatment rates may be a reflection of local treatment practices rather than a response to disease severity, with data showing rates of appropriate prescribing and compliance with antibiotic guidelines in ACT hospitals to be the lowest in Australia during the study period [42].

One-third of *Campylobacter*-associated hospitalisations received antibiotics, either empirically or as targeted therapy for confirmed campylobacteriosis. Second generation fluoroquinolones—mainly per oral ciprofloxacin—comprised 80% of treatment, with macrolides the remainder. Australia has been successful in efforts to limit use of quinolones in humans and to prohibit their use in food-producing animals [30]. This has preserved their clinical use in Australia, with ciprofloxacin and norfloxacin remaining as empirical treatment options for acute infectious diarrhoea, while being recommended alongside azithromycin for treatment of domestically acquired *Campylobacter* enteritis [40]. Conversely, the high rates of quinolone resistance experienced in the UK, EU and US has seen macrolide treatment recommended or a greater emphasis placed on travel history and knowledge of local resistance patterns to guide empirical prescribing [43, 44].

Within our hospitalised study population, the strongest predictor of antibiotic treatment was collection of a blood specimen for culture. Both antibiotic prescription and ordering of blood cultures are clinical decisions, suggesting that the underlying clinical context observed by treating clinicians impacts both practices inducing them to be positively associated. Admission under specific clinical units, including Gastroenterology, Infectious Diseases and General Medicine were also associated with increased odds of receiving antimicrobial therapy. Hospitalisation implies a higher level of morbidity, potentially explaining the higher likelihood

of antibiotic administration. Variation in treatment focus could also be expected between subspecialties, especially when underlying comorbidities are exacerbated. Such decision making may be further influenced by routine clinical behaviour, unease regarding the consequences of BSI or by the acceptability of not obtaining blood cultures among particular specialities [4].

Age was also found to be an important factor in treatment, with paediatric admissions being less likely to receive antibiotics. This finding reflects that fluoroquinolones—the most commonly prescribed antibiotic class—are not recommended for use in children due to safety concerns [45]. We also observed that patients aged 40–49 years were more likely to be prescribed antibiotics. Reasons for this are less certain, but around 20% of admissions to high prescribing units such as Gastroenterology and Infectious Diseases were in this age range.

Vomiting and electrolyte imbalance were also associated with provision of antibiotic therapy. Vomiting is a less frequently reported symptom of campylobacteriosis but serves as an indicator for disease severity [46] and a predictor of bacteraemia [47]. While we did not assess the severity of dehydration, it is likely that a population such as ours included a higher proportion of cases with more pronounced symptomatology and severity of symptoms compared with non-hospitalised cases.

Limitations

There are a number of potential limitations with our study. Firstly, our rates of bacteraemia may underestimate the true incidence, as we identified cases using only public hospital laboratory data. Other cases of *Campylobacter* bacteraemia may have been diagnosed and managed in the community or the private hospital sector, although the clinical significance of these is less certain. A second limitation relates to the precision of our model estimates, with the small numbers of observations for some outcomes making detection of clinically meaningful associations challenging. Despite this, the observed associations still align plausibly with *Campylobacter*'s epidemiology. A third limitation relates to the generalisation of our findings. Our study population was hospital-based and drawn from a single Australian territory, with regional and international differences in the epidemiology of campylobacteriosis being observed in high income settings [14, 22, 48]. Finally, antimicrobial susceptibility testing and bacterial speciation were not performed on all isolates, limiting exploration of species-specific features such as higher macrolide resistance rates among *C. coli* isolates [49].

Conclusions

Campylobacter infections cause a substantial disease burden, as reflected by the high number of hospitalisations and high incidence of bacteraemia in our study. While a spectrum of illness can be observed among hospitalisations, many cases exhibit signs suggestive of systemic disease. Furthermore, both the proportion of cases receiving antibiotic treatment and those having isolates that were non-susceptible to standard antimicrobials increased over time. Given the increasing incidence of *Campylobacter* infections, particularly among older patients, understanding hospitalisation burden becomes increasingly important. This study provides some evidence in relation to clinical factors influencing the management of hospitalised cases in high income settings.

Abbreviations

ACT: Australian Capital Territory; aOR: Adjusted Odds Ratio; BSI: Blood Stream Infection; CI: Confidence Interval; EU: European Union; ICD: International Classification of Diseases; UK: United Kingdom; US: United States.

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Authors' contributions

CM planned the study, undertook data collection, performed analysis and drafted the manuscript. BO provided specific advice on analyses. CM, KK, BO, LS and MK all contributed to and approved the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the ACT Government Health Directorate and Calvary Health Care (Bruce). Restrictions apply to the availability of these data, which were used under approvals for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ACT Government Health Directorate and Calvary Health Care (Bruce).

Declarations

Ethics approval and consent to participate

Ethics approvals were obtained from the Human Research Ethics Committee of the ACT Government Health Directorate (Ref. ETHLR14.121), Calvary Health Care (Bruce) (Ref. 22-2014) and the Australian National University (Ref. 2014/223). These approvals included permission to access inpatient medical records subject to the study data set being anonymised before use. Individual patient consent was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

Author details

¹National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, 2602 Canberra, ACT, Australia. ²Department of Microbiology, Canberra Hospital and Health Services, Canberra, ACT, Australia. ³School of Public Health, University of Queensland, Brisbane, QLD, Australia.

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CASE REPORT

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First case report of myopericarditis linked to *Campylobacter coli* enterocolitis

Cameron R. M. Moffatt^{1*}, Soniah B. Moloi² and Karina J. Kennedy³

Abstract

Background: *Campylobacter* spp. are a common cause of mostly self-limiting enterocolitis. Although rare, pericarditis and myopericarditis have been increasingly documented as complications following campylobacteriosis. Such cases have occurred predominantly in younger males, and involved a single causative species, namely *Campylobacter jejuni*. We report the first case of myopericarditis following *Campylobacter coli* enterocolitis, with illness occurring in an immunocompetent middle-aged female.

Case presentation: A 51-yo female was admitted to a cardiology unit with a 3-days history of chest pain. The woman had no significant medical history or risk factors for cardiac disease, nor did she report any recent overseas travel. Four days prior to the commencement of chest pain the woman had reported onset of an acute gastrointestinal illness, passing 3–4 loose stools daily, a situation that persisted at the time of presentation. Physical examination showed the woman's vital signs to be essentially stable, although she was noted to be mildly tachycardic. Laboratory testing showed mildly elevated C-reactive protein and a raised troponin I in the absence of elevation of the serum creatinine kinase. Electrocardiography (ECG) demonstrated concave ST segment elevations, and PR elevation in aVR and depression in lead II. Transthoracic echocardiogram (TTE) revealed normal biventricular size and function with no significant valvular abnormalities. There were no left ventricular regional wall motion abnormalities. No pericardial effusion was present but the pericardium appeared echodense. A diagnosis of myopericarditis was made on the basis of chest pain, typical ECG changes and troponin rise. The chest pain resolved and she was discharged from hospital after 2-days of observation, but with ongoing diarrhoea. Following discharge, a faecal sample taken during the admission, cultured *Campylobacter* spp. Matrix assisted laser desorption ionization time-of-flight (Bruker) confirmed the cultured isolate as *C. coli*.

Conclusion: We report the first case of myopericarditis with a suggested link to an antecedent *Campylobacter coli* enterocolitis. Although rare, myopericarditis is becoming increasingly regarded as a complication following campylobacteriosis. Our report highlights potential for pericardial disease beyond that attributed to *Campylobacter jejuni*. However uncertainty regarding pathogenesis, coupled with a paucity of population level data continues to restrict conclusions regarding the strength of this apparent association.

Keywords: *Campylobacter* infections, *Campylobacter coli*, Myopericarditis, Etiology, Female, Case report

Background

Campylobacter species are among the most widespread and commonest cause of bacterial enterocolitis worldwide [1]. *C. jejuni* is recognised as the leading cause of human illness, although *C. coli* might account for up to 25% of *Campylobacter* enterocolitis [2]. Complications such as bacteraemia or the development of post-infectious sequelae

have an established place in the epidemiology of campylobacteriosis, with cardiac complications being less commonly reported [1]. We describe what we believe to be the first case of myopericarditis associated with *C. coli* enterocolitis and discuss the epidemiology and pathogenesis of this condition.

Case presentation

A 51-yo female was admitted to the cardiology unit of an Australian public hospital with a 3-day history of continuous, dull, non-radiating, non-pleuritic, left lateral chest pain, with associated diaphoresis, nausea, palpitations and

* Correspondence: cameron.moffatt@anu.edu.au

¹National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra 2602, ACT, Australia
Full list of author information is available at the end of the article



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pre-syncope. Some relief of chest pain was achieved by leaning forward. Administration of combined paracetamol and codeine phosphate also relieved the pain. Four days prior to the commencement of chest pain the woman had reported onset of an acute gastrointestinal illness, passing 3–4 loose stools daily. This diarrhoea was persistent at the time of presentation. The woman had no significant medical history or risk factors for cardiac disease, nor did she report any recent overseas travel.

Physical examination showed the woman to be afebrile but mildly tachycardic, with a heart rate of 106 bpm. Blood pressure was 120/76 mm Hg. Examination of the chest revealed normal heart sounds, without any murmur or rub. Jugular venous pressure was normal. Pulmonary examination was normal with no signs of respiratory distress (RR 18), although mild tachypnea was noted during the course of her admission. The abdomen was soft and non-tender.

Laboratory testing showed a mildly elevated C-reactive protein (30.0 mg/L; normal range <5.0 mg/L) and a raised troponin I (maximal value 70 ng/L at the time of emergency department presentation; normal range <16) in the absence of elevation of the serum creatinine kinase. Liver enzymes were mildly elevated with an ALT 65 U/L (normal range <55 U/L) and ALKP 142 U/L (normal range 20–110 U/L). Full blood count and serum electrolytes were unremarkable.

Serial electrocardiographs demonstrated concave ST segment elevations involving leads I, II, III, aVF and V6, PR elevation in aVR and PR depression in lead II (Fig. 1). Differential diagnoses of completed acute myocardial infarction or pericarditis secondary to recent diarrhoeal illness were made, with the woman initially managed for

an acute coronary syndrome with subcutaneous clexane 70 mg bd, aspirin 100 mg daily, clopidogrel 75 mg daily and metoprolol 25 mg bd prior to expert cardiology review and echocardiogram. Transthoracic echocardiogram (TTE) revealed normal biventricular size and function with no significant valvular abnormalities. No pericardial effusion was present but the pericardium appeared echodense and thickened. A diagnosis of myopericarditis was made.

Clexane and clopidogrel were ceased and colchicine 500mcg bd commenced. The chest pain resolved and she was discharged from hospital after 2 days, but with ongoing diarrhoea. Following hospital discharge, a faecal sample taken during the admission, cultured *Campylobacter* spp. in isolation. Matrix assisted laser desorption ionization time-of-flight (Bruker) confirmed the cultured isolate as *C. coli*.

Discussion

Acute pericarditis is a not uncommon, frequently idiopathic disorder that mostly follows a benign clinical course. Some myocardial involvement often accompanies acute pericarditis, with the term myopericarditis indicating the pericardium as the primary focus [3]. Viruses are often implicated when acute pericarditis or myopericarditis are linked to infection, with bacterial causes less commonly described [3]. Diagnostic criteria for acute pericarditis include chest pain, pericardial friction rub, ST segment elevations and pericardial effusion, with a clinical diagnosis made when two of these criteria are met [3]. A clinical diagnosis of myopericarditis includes the additional detection of elevated cardiac enzymes or a new onset of depressed left ventricular systolic function [3].

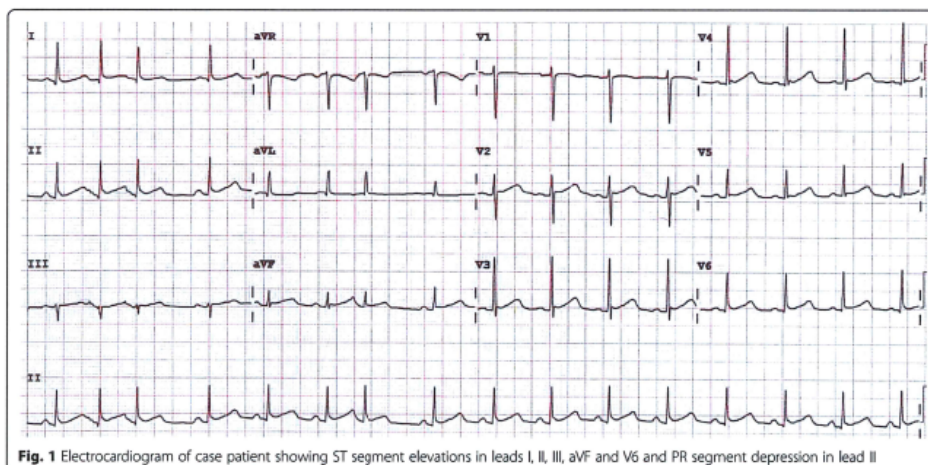


Fig. 1 Electrocardiogram of case patient showing ST segment elevations in leads I, II, III, aVF and V6 and PR segment depression in lead II

Campylobacter spp. have an uncommon but increasingly recognised link with myopericarditis, as supported by a growing body of case reports and reviews of literature [4–6]. Our report is notable in terms of the observed differences in both pathogen and host characteristics. Firstly, our patient was positive for *C. coli*, a species well recognised as a cause of enterocolitis, but not previously reported in association with myopericarditis. Secondly, the patient was a healthy, middle-aged female, in contrast to previous patients where most were younger immunocompetent males [4–6]. Although *Campylobacter* does show tendency to cause higher rates of disease in men compared to women, the apparent predilection towards men in myopericarditis is striking. However despite this observation, epidemiological evidence of a causal association between campylobacteriosis and myopericarditis is lacking. We identified a single study that showed a greater incidence of myocarditis in *Campylobacter* positive cases than controls at 16.1 cases per 100,000 person-years (95% CI 2.3–114.4) compared to 1.6 cases per 100,000 person-years (95% CI 0.2–11.4), but the result was not significant and absolute case numbers were small [7].

It is important to make distinction between myopericarditis associated with *C. jejuni* or *C. coli* and that with *C. fetus*. The former are recognised causes of enteric disease in humans and likely represent archetypal causes of *Campylobacter* myopericarditis. Conversely *C. fetus* is an atypical, invasive species, capable of evading the host immune system by means of complement resistant surface proteins [8]. As such it is more frequently isolated from blood and pericardial fluid, with enteric symptoms either absent or less pronounced [9]. For *C. jejuni* (and *C. coli*) associated myopericarditis, the putative mechanisms include direct infection of the pericardium or myocardium, an immune hypersensitivity reaction, or the effect of bacterial toxins [10]. Currently evidence for direct infection is limited to two reports of *C. jejuni* detection in pericardial fluid [11, 12]. A dominant immune-mediated response also seems less likely given the short window between the onset of enteric and cardiac symptoms, as distinct to that seen with *C. jejuni* and development of other immune-mediated disease (e.g., Guillain-Barré syndrome and reactive arthritis) [10]. Although there is a lack of evidence for a specific *Campylobacter*-associated cardiotoxin [13], the short window period surely favors a toxin-mediated mechanism [4, 6]. Furthermore, the infrequency of *C. coli* myopericarditis as highlighted by our case might possibly be explained by the dominance of *C. jejuni* at the species level, along with the lower incidence of cytotoxin and enterotoxin production by *C. coli* compared to *C. jejuni* [13].

It is unclear whether antibiotic treatment influences the outcome of *Campylobacter* spp. myopericarditis,

however a recent examination of *C. jejuni*-associated myopericarditis cases showed treatment with either macrolide or fluoroquinolone antibiotics to be a common practice although without any apparent consensus on dosage and treatment duration [5]. However campylobacteriosis is generally regarded as a self-limiting illness with antimicrobial therapy recommended for immunocompromised patients, patients whose symptoms are severe or persistent, or who develop extra-intestinal infections [1]. For our case confirmation of *Campylobacter* spp. in stool occurred following hospital discharge, with a mechanism for myopericarditis such as direct infection or toxin-mediated response not able to be readily determined. As such antimicrobial therapy was not commenced. Treatment for the myopericarditis was conservative, using nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. Among case reports describing *Campylobacter*-associated myopericarditis we identified a single episode where colchicine, as an adjunctive to aspirin, was used in treating myopericarditis, with the case reported as fully recovered at a 3-month review [14]. Anecdotally, clinical outcomes for *C. jejuni* (and *C. coli*) associated myopericarditis appear favourable [5] with low rates of morbidity, mortality, evolution to heart failure and worsening ventricular function [15].

Conclusion

We report the first case of myopericarditis linked to a *C. coli* enterocolitis, with the illness running a benign clinical course. While increasingly recognised as a complication of campylobacteriosis, the paucity of population level data restricts further conclusions on the strength of any association between *Campylobacter* infection and myopericarditis. Further, the mechanism(s) of pathogenesis also remain uncertain, although anecdotally may favour a toxin-mediated response.

Abbreviations

ALP: Alkaline phosphatase; ALT: Alanine transaminase; CI: Confidence interval; ECG: Electrocardiography; RR: Respiratory rate; TTE: Trans-thoracic echocardiography

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Availability of data and materials

Not applicable.

Authors' contributions

CM identified the case, obtained the image for the figure and drafted the manuscript. SM reviewed the cardiology diagnosis and associated testing (including electrocardiographies and echocardiograms) and drafted the manuscript. KK reviewed the microbiological diagnosis, obtained patient consent and drafted the manuscript. All authors read and approved the final manuscript.

Authors' information

CM is a PhD candidate at the Australian National University. He has a background in communicable disease epidemiology, with a particular interest in gastrointestinal infections of public health importance. His thesis is concerned with clinical outcomes following *Campylobacter* infection.

Competing interests

The authors declare they have no competing interests.

Consent for publication

Informed consent was obtained from the patient for publication of this case report.

Ethics approval and consent to participate

Ethics approval to undertake a retrospective study of hospitalisation linked to *Campylobacter* infection was obtained from the Human Research Ethics Committees of the ACT Government Health Directorate (Ref. ETHLR.14.121) and the Australian National University (Ref. 2014/223). Individual consent to participate was not required.

Author details

¹National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra 2602, ACT, Australia. ²Department of Cardiology, Canberra Hospital and Health Services, Canberra 2605, ACT, Australia. ³Department of Microbiology, Canberra Hospital and Health Services, Canberra 2605, ACT, Australia.

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Chapter 5 - Discussion

Through the preceding chapters, I have considered three key components of *Campylobacter*'s epidemiology, namely the incidence of disease, the potential for outbreaks and the severity of outcomes via examination of hospitalisations. My exploration of these themes has enabled a consideration of both the public health and clinical aspects of this common enteric pathogen. It is apparent from the studies presented that both public health and clinical medicine share a large disease burden, however much of this burden is disguised by the sporadic nature of infection, the physiology of the organism and the capacity of health systems to link cases to outcomes.

In Chapter 2, the incidence of *Campylobacter* infection in Australia was shown to be high in relation to comparable international settings. Typical of *Campylobacter*'s epidemiology was the finding of increased rates of disease in males and a seasonality characterised by rising case numbers during the southern hemisphere spring. Age distribution was tri-modal, with crude incidence highest in those aged <5 years, between 20-40 years and those over 65 years, with increasing incidence predicted for older age-groups.

Chapter 3 demonstrated that outbreaks of campylobacteriosis were infrequent events in Australia, with no evidence of any increase in events during the study period. While the emergence of poultry-liver containing foods was identified as a risk, the relative contribution of raw dairy products or waterborne transmission was much less than in other high-income settings. However gaps in understanding transmission dynamics remain, mainly due to the challenges of conducting detailed investigations in settings like aged-care.

In Chapter 4, using linked hospital administrative data and microbiology data, it was shown that *Campylobacter*-associated hospitalisations were a considerably underestimated health outcome. The review of admission characteristics also revealed a broad spectrum of illness ranging from uncomplicated enterocolitis through to more severe manifestations such as

bacteraemia. Among admissions, trends in increasing antibiotic use, along with increasing levels of clinical isolate non-susceptibility to standard antimicrobials were also observed. Numerous explanatory factors were identified as being important in the investigation and management of hospitalised cases, including aspects of clinical presentation, the presence of certain comorbidities, the development of complications and the increasing age of cases.

The manuscripts accompanying the thematic chapters include broad discussions of study-specific results in the context of *Campylobacter* infections in high-income settings. While the themes may appear disparate for the purposes of an overall discussion, significant insight into the epidemiology of *Campylobacter* spp. can be obtained through considering them *in toto*. To that end, a common feature identified across all three themes is the relationship between increasing age and risk of campylobacteriosis.

The predicted increase in incidence of campylobacteriosis among older Australians over time is supported by international analyses of disease incidence, with data from England and Wales suggesting a change in the age structure of infections, with older persons becoming the population most at risk [1, 2]. Like most developed countries, Australia's population is ageing as a result of sustained low fertility and increasing life expectancy [3], in addition to social factors such as the post-Second World War baby boom. In 2017, 3.8 million Australians (15%) were aged 65 years and over, with this projected to increase to 8.8 million (22%) by 2057 [4]. Specific age-related contributors to increased susceptibility to infections include a weakening of the immune system, gastrointestinal tract changes, higher prevalence of comorbidities and more frequent use of antacids and immune suppressant medication [5].

A probable driver of disease incidence, including higher rates among older Australians, is a lack of public awareness of campylobacteriosis as a public health issue. Previous studies conducted in Australia and other high-income settings have revealed a high proportion of

respondents were unaware of *Campylobacter* and its role as a major foodborne pathogen. The risk to the elderly of foodborne illness acquired via the inappropriate handling of raw poultry is well established, with experts identifying the washing of knives, cutting boards and preparation surfaces with hot water and detergent being especially important [6]. Targeted interventions aimed at improving knowledge and understanding of safe food handling among the elderly will form an important aspect in reducing disease incidence among this group. One potential approach to this is through use of trusted information sources, e.g. healthcare providers, to deliver information and raise awareness of food safety issues with older patients [7].

In Australia, ACFs are common settings for gastroenteritis outbreaks, although the majority of events involve likely person-to-person transmission of viral pathogens [24].

Campylobacter spp. have previously been observed as causing outbreaks in ACFs [20], with these now becoming the most common setting for campylobacteriosis outbreaks in Australia as described in Chapter 3. Elderly persons residing in ACFs are particularly susceptible to outbreaks of infectious diseases not only because of the physiological changes that accompany ageing and the effects of comorbidities but also because of the physical and cultural characteristics of the facilities in which they live [8, 9]. The vulnerability of this subpopulation has been brought into stark relief most recently with the high attack rates and case fatality rates seen among elderly ACF residents with COVID-19 disease [10].

In high-income countries, burden of disease estimates suggest *Campylobacter* has a low associated mortality [11, 12]. However such estimates lack consideration of comorbidity and ageing on death. Previously, a Danish study demonstrated significant excess long-term mortality among the elderly up to one year post *Campylobacter* infection [13]. In the US, persons aged ≥ 65 years have been shown to be at greatest risk of death due to diarrheal illness [14], with nursing home residents comprising a disproportionate number of fatal cases

[15, 16]. Given the health status of ACF residents, relative mortality can be significant in this setting. While few in absolute number, it is nevertheless telling that all Australian *Campylobacter* outbreak-associated deaths occurred among elderly ACF residents [17].

Foodborne transmission was identified as causing a number of ACF outbreaks, highlighting the importance of food safety protocols. Under Food Standards Australia New Zealand's Standard 3.3.1, ACFs are required to develop and implement HACCP-based (Hazard Analysis Critical Control Point) food safety programmes to protect vulnerable residents [18]. A positive finding from Australian data has been a lower incidence of *Campylobacter* infections among ACF residents compared with community dwelling persons aged ≥ 65 years, suggesting the impact of food safety regulation in ACFs and higher infection risk for elderly persons preparing food at home [19].

Investigating outbreaks of bacterial gastroenteritis in ACFs can be challenging [17]. Review of evidence supporting foodborne transmission resulted in numerous outbreaks being reclassified as having an unknown transmission source. This finding highlights the importance for investigators to actively exclude other routes of transmission, in particular direct zoonotic transmission from animals either visiting or residing in ACFs [20].

In comparison to non-admitted community cases, persons hospitalised with *Campylobacter* infection were observed to be significantly older. Rates of admission also increased incrementally with age, most notably for those aged ≥ 60 years. This feature is consistent with the epidemiology of campylobacteriosis in a variety of high-income settings including Germany, New Zealand and Scotland where elderly persons have the highest rates of hospitalisation [21-23].

Among *Campylobacter*-associated admissions, correlations between increasing patient age and length of stay and level of comorbidity were observed. These findings reflect the results

from other *Campylobacter*-specific studies showing comorbidity and age ≥ 60 years to be independently associated with hospitalisation [24]. While it has been suggested cases with co-morbidities will be more likely to seek health care for gastrointestinal symptoms, including faecal specimen testing, than those without comorbidities [24], the generalisability of this to a hospitalised population remains to be proven. The relevant importance of comorbidity over age has been disputed, with some research showing age as the only independent factor associated with hospitalisation [25]. Overall the levels of comorbidity described in the ACT hospitalisation study were similar to those of other studies describing patients hospitalised with gastroenteritis [26]. A correlation between increasing age and increasing time to hospital admission was also observed, although this did not appear to translate into prolonged LOS or adverse clinical outcomes. For persons hospitalised following acute gastrointestinal illnesses there is currently limited data available on factors influencing treatment delays [27].

While predominantly causing acute enterocolitis, *Campylobacter* infection may result in a variety of complications ranging from localised infection to disseminated spread or post-infectious sequelae [28]. One of the most important extra-gastrointestinal manifestations of *Campylobacter* species is bacteraemia, which is predominantly associated with *C. jejuni*, *C. coli*, and *C. fetus* infections [28]. At a population level bacteraemia is a rare manifestation, more likely to occur among patients who are immunocompromised or either very young or very old [29]. In the UK and US, blood isolates have been reported as accounting for 0.15% and 0.26% of all *Campylobacter* isolates [30, 31], while a Danish registry based study estimated the incidence of *Campylobacter* bacteraemia at 2.9 per 1 million person-years [32]. While advanced age has been statistically associated with bacteraemia [32], other population level data have suggested *Campylobacter* spp. bacteraemia predominately affects younger individuals without major underlying diseases [33]. In the ACT hospitalisation study

modelling suggested the strongest explanatory variables for bacteraemia were advanced age and concurrent illnesses. However a quarter of *Campylobacter* blood stream infections described in Chapter 4 were likely transient episodes, involving younger cases without evidence of comorbidity or concurrent pathology. An earlier Australian study examining hospitalised cases of *Campylobacter* enteritis reported a bacteraemia rate of 1.6% (14/885) [34]. This was noticeably lower than the 7.5% positive blood culture rate observed in the ACT hospitalisation study. Such differences could be due to changes in blood culture protocols and systems, highlighting a potential for *Campylobacter* bacteraemia to be underestimated [35]. However the clinical significance of additional cases detected via universal blood culturing of hospitalised cases is perhaps less certain, given they may represent transient episodes of bacteraemia as suggested in the ACT study.

In high-income settings, age has been identified as the most important risk factor for death among cases hospitalised with diarrhoeal illness, although *Campylobacter*-specific mortality is still regarded as being low [30, 36]. For *Campylobacter* bacteraemia, especially in patients with concurrent pathologies, deaths within 30 days of diagnosis have been reported to be as high as 10-15% [28]. There is also evidence to suggest that medium and long term mortality is impacted (e.g. deaths within 6 months or a year) among elderly persons hospitalised with *Campylobacter* infection [37]. Despite a high incidence of bacteraemia among the study group, no associated inpatient deaths were observed, while overall inpatient mortality among *Campylobacter*-associated admissions was low (0.15%). The lower mortality associated with *Campylobacter* infections has been linked to the reduced propensity of common species to cause invasive disease [36].

In addition to bacteraemia and other localised, reactive and post-infectious complications of *Campylobacter* spp., the ACT hospitalisation study showed numerous cases experienced significant derangement in their vital signs and exacerbations of underlying health conditions.

The prevalence of electrolyte disturbances, renal dysfunction and hypotension were all higher among older admissions. Acute exacerbations of chronic conditions were notable, in particular underlying kidney disease. This aligns with evidence showing increased risk of renal impairment among hospitalised gastroenteritis cases, including those with antecedent *Campylobacter* infection and pre-existing kidney disease [38, 39].

Rates of antimicrobial prescribing among the hospitalised elderly are considerable in high-income settings, with point-prevalence surveys showing significantly higher prescribing for patients aged ≥ 75 years higher when compared to an adult reference population aged 18–64 years [40]. Although infections per se in the elderly can be more frequent and severe [41] rates of antibiotic prescribing could also be expected to differ when considering the site of infection or involvement of a self-limiting pathogen such as *Campylobacter*. In the ACT hospitalisation study cases receiving antibiotics were significantly older than cases who did not receive antibiotics. However the percentage of *Campylobacter*-associated admissions aged ≥ 75 years who received antibiotics (39%) did not differ significantly to the 35% of admissions aged 18–65 years who received antibiotics. While older age was not identified as an independent explanatory factor for antibiotic treatment, the ACT study did show a significant negative association with antibiotic treatment for cases aged < 20 years. This finding reflects ciprofloxacin's use in children being contraindicated [42].

Overall, the impact of age and associated frailty on clinical outcomes among hospitalised cases is evidenced by increased admission rates, LOS, risk of extra-intestinal disease and exacerbations of underlying health conditions. Given the projected increase in the proportion of elderly persons living in high-income settings, associated morbidity, including hospitalisation due to *Campylobacter* spp. can be expected to increase. Cost considerations are also important with those ≥ 65 years already having the highest rates of general practice consultation and hospitalisation for acute gastroenteritis [43]. This transition to higher rates

of disease in older persons carries significant implications for public health and clinical care. As such there is a need for improved understanding of risk factors specific to older Australians, combined with targeted public health messaging to educate this group of increased disease risk.

In addition to highlighting some of the recognised complexities and characteristics of *Campylobacter*'s epidemiology, this research has identified a number of areas of public health and clinical concern warranting further investigation. Briefly these include addressing disease risk among elderly Australians, better understanding outbreak transmission in aged-care, understanding predictors of hospitalisation, determining rates of antibiotic use between hospitalised and community cases, and quantifying associations between *Campylobacter* infection and complications including myopericarditis and acute kidney injury.

In conclusion, Australia experiences a high incidence of campylobacteriosis with rates of disease being predicted to increase significantly among a growing elderly population. In spite of the high incidence of disease, outbreaks have been proven to be relatively uncommon events. Conversely, the extent of hospitalisation associated with this common enteric infection appears to be significantly underestimated. While *Campylobacter* infections have the capacity to cause suffering across all strata of Australian society, an increasingly disproportionate share of the public health and clinical burden will likely be carried by those who are particularly vulnerable, namely elderly and older Australians.

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