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Reactive Arthritis Surveillance following a Large Waterborne Campylobacteriosis Outbreak in Havelock North, New Zealand

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Abstract

Objectives

In August 2016, *Campylobacter* spp. contaminated the untreated reticulated water supply to Havelock North, New Zealand resulting in a large-scale gastroenteritis outbreak affecting an estimated 8,320 people. We aimed to determine the incidence of probable reactive arthritis (ReA) cases in individuals with culture-confirmed campylobacteriosis (CC), self-reported probable campylobacteriosis (PC), and those reporting no diarrhea (ND).

Methods

We enrolled notified CC cases with gastroenteritis symptom onsets 5 August – 6 September 2016 and conducted a telephone survey of households supplied by the contaminated water source to enrol PC and ND cases. We identified cases with new ReA symptoms using an adapted Acute Reactive Arthritis (AReA) telephone questionnaire. Those reporting ≥1 symptom underwent a telephone interview with the study rheumatologist. Probable ReA was defined as spontaneous onset of pain suggestive of inflammatory arthritis in ≥ 1 previously asymptomatic joint for ≥ 3 days occurring ≤ 12 weeks after outbreak onset.

Results

One hundred and six (47.3%) CC, 47 (32.6%) PC, and 113 (34.3%) ND cases completed the AReA telephone questionnaire. Of those reporting ≥1 new ReA symptom, 45 (75.0%) CC, 13 (68.4%) PC, and 14 (82.4%) ND cases completed the rheumatologist telephone interview. Nineteen CC, 4 PC, and 2 ND cases developed probable ReA, resulting in minimum incidences of 8.5%, 2.8%, and 0.6% and maximum incidences of 23.9%, 12.4%, and 2.15%.

Discussion

We describe high probable ReA incidences among gastroenteritis case types during a very large *Campylobacter* gastroenteritis outbreak using a resource-efficient method that is feasible to employ in future outbreaks.

Keywords: Reactive arthritis, epidemiology, infections

Strengths and Limitations of this study

Strengths

- Reported Campylobacteria-associated ReA rates vary due to different methodologic approaches that limit inclusion to one gastroenteritis type (self-reported versus culture-proven).
- To address these limitations, we estimated the incidence and characterized the clinical presentations of probable ReA cases in three groups: individuals with culture-confirmed campylobacteriosis, those with self-reported gastroenteritis, and those reporting no diarrhoea during a large campylobacteriosis outbreak
- We offer a comprehensive description of ReA rates based on gastroenteritis severity to guide practitioners.

Limitations

- Cases were not examined by a rheumatologist; classification of joint involvement was dependent on a patient's self-report, preventing definitive diagnosis of ReA

INTRODUCTION

Reactive arthritis (ReA) is a known post-infectious sequelae of *Campylobacter* gastroenteritis with a clinical spectrum ranging from transient arthralgias to severe peripheral and/or axial arthritis with occasional extra-articular features.[1, 2] Estimates of ReA incidence following *Campylobacter* infection vary widely from 1–26%.[2-7] This wide variation is likely due, in part, to lack of a standard definition for ReA and varying methods for estimating ReA incidence.[6] Population-based studies have estimated ReA incidence by sampling individuals with culture-proven bacterial gastroenteritis;[1, 2, 4] however, it is estimated that less than a quarter of gastroenteritis cases seek medical consultation and only 50% of those have a faecal specimen cultured.[8] This method likely underestimates ReA incidence. Furthermore, there is often a delay between gastroenteritis development and investigation for ReA,[9, 10] which may reduce capture of ReA cases.

Outbreak-based studies allow estimation of ReA incidence in a cohort of exposed individuals; however, many studies use self-reported gastroenteritis because culture confirmation can exceed laboratory capacity during a large outbreak.[3, 11-13] Some outbreak-based studies have calculated ReA incidence exclusively in culture-positive gastroenteritis cases.[14, 15] Both approaches typically rely on data from exposed individuals who sought medical care, excluding cases with less severe presentations, and thereby limiting not only ReA incidence estimates, but potentially narrowing the described clinical spectrum of ReA in the affected population.

During 5–12 August 2016, the untreated reticulated water supply to Havelock North, New Zealand became contaminated with sheep faecal matter following a heavy rainfall event. This resulted in a narrow exposure outbreak of *Campylobacter spp*. gastrointestinal infections,

affecting an up to 8,320 people. [16] To address the above-mentioned limitations of previous ReA epidemiologic studies, we aimed to estimate the incidence and characterize the clinical presentations of probable ReA cases in three groups; individuals with culture-confirmed campylobacteriosis, those with self-reported probable gastroenteritis, and those reporting no diarrhoea during the outbreak period.

METHODS

Cohort Description

The Hawke's Bay District Health Board (HBDHB) provides medical care and public health services for approximately 164,000 people in a 14,000 square kilometre area, including metropolitan and rural populations. The catchment area includes Havelock North, which has a population of 14,118 and its own reticulated drinking water derived from untreated ground water. Prospective, population-based surveillance for acute gastrointestinal illnesses was conducted among residents of the HBDHB catchment area during 13 August – 6 September 2016, and faecal specimens were submitted to local laboratories for culture.[16] Additionally, we conducted active surveillance through four rounds of telephone survey. We randomly sampled the same panel of 250 Havelock North households supplied by the contaminated municipal water source. The last survey occurring 7 weeks following the outbreak onset to identify additional gastroenteritis infections among residents who did not seek healthcare as well as identify exposed individuals who did not develop diarrhoea.

Patient and public involvement

Local community leaders were consulted in the design of this study to ensure outcomes met the priorities of the community. Preliminary communication about this study were distributed by the local media to the public to inform the population of the impact of this outbreak.

Campylobacter gastroenteritis outbreak case definitions

The study population included three groups. A confirmed campylobacteriosis (CC) case was defined as an individual who consumed reticulated water from Havelock North, New Zealand from 5 – 12 August 2016 with clinician-confirmed diarrhoea between 5 August – 6 September 2016 with a positive faecal specimen for *Campylobacter* spp. A probable campylobacteriosis (PC) case was defined as an individual from the household telephone survey with the same exposure as a CC case who developed diarrhoea between 5 August – 6 September 2016 without presentation to healthcare or provision of faecal specimen. No diarrhoea participants (ND cases) were also identified by the household telephone survey and had the same exposure to contaminated water as a PC case but did not develop diarrhoea between 5 August – 6 September 2016. Seven weeks after the outbreak onset, all eligible cases were contacted by telephone to consent for enrolment into ReA surveillance.

ReA screening questionnaire and rheumatologist interview

Using an adapted version of the previously validated Acute Reactive Arthritis (AReA) questionnaire,[14] (Supplementary Appendix 1) we administered a ten-question telephone survey through a commercial survey provider to ReA surveillance enrolees eight weeks after the outbreak onset. To comply with case definitions, we excluded 7 CC cases from the survey who denied a history of diarrhoea during the outbreak. All ages were included; parents or guardians provided proxy responses for children aged <15 years. Approximately 12 weeks after outbreak onset, respondees reporting ≥1 symptom on the AReA questionnaire underwent a telephone interview with the study rheumatologist, RG, who has 15 years' experience in rheumatology practice. Participants were asked about the inflammatory nature and onset of joint symptoms. (Supplementary Appendix 2). The study rheumatologist defined a probable ReA case as spontaneous onset of pain suggestive of inflammatory arthritis in ≥ 1 previously

asymptomatic joint for ≥ 3 consecutive days occurring ≤ 12 weeks after outbreak onset in a CC, PC, or ND cases.

Ethics

New Zealand Health and Disabilities Ethics Committee approval was obtained prior to study enrolment.

Data analysis

Differences in baseline characteristics between outbreak case types were assessed using chi-square or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. Minimum ReA rates are reported as the proportion of probable ReA cases occurring out of the total number of residents eligible for enrolment for each outbreak case type. Maximum ReA rates were estimated by applying the proportion of probable ReA cases occurring in residents who reported ≥1 ReA symptoms on the screening survey that completed the rheumatologist interview to those who reported ≥1 ReA symptoms but failed to complete the rheumatologist interview, then dividing the sum by the population that completed the screening survey. This was calculated for each outbreak case type individually. Relative risk (RR) and 95% confidence intervals (CI) were calculated to assess the risk of developing probable ReA among outbreak case types and among adults compared with children. P-values ≤0.05 were considered significant. Data were analysed using SAS 9.4.

RESULTS

A total of 232 CC cases were notified to HBDHB. Of these, 114 (49.1%) participated in the AReA screening telephone questionnaire at 8 weeks; however, 8 responders reported no history of diarrhoea and were excluded from the remainder of the questionnaire, leaving 106 (47.3%)

of 224 eligible CC cases completing the AReA questionnaire (Figure 1). A total of 144 PC and 329 ND cases were identified from the randomly sampled household survey of which 47 (32.6%) PC and 113 (34.3%) ND cases completed the AReA questionnaire. Forty-three (40.6%) CC, 16 (34.0%) PC, and 11 (9.73%) ND cases reported new joint symptoms after outbreak onset. New extra-articular symptoms including heel pain, eye symptoms, mouth ulcers, genital rash or discharge, or palm or sole rash were reported by 42 (39.6%) CC, 12 (25.5%) PC, and 12 (10.6%) ND cases.

PC and ND cases were older ($p<0.001$) and more likely to be female ($p<0.001$) compared with CC cases (Table 1). CC cases were more likely to be of Maori or Pacific ethnicities than PC and ND cases ($p<0.01$). CC cases had longer duration of gastroenteritis symptoms (fever, nausea, vomiting, abdominal pain) (median= 10 days) compared with PC (median=7 days) and ND cases (median=3 days) ($p=0.0014$). More CC cases had new joint ($p<0.001$) and extra-articular symptoms ($p<0.001$) compared with ND cases. There were no differences between CC and PC cases for joint or extra-articular symptoms.

The rate of new ReA symptoms was higher among CC (RR 3.76; 95% CI: 2.35 – 6.01) and PC cases (RR 2.26; 95% CI: 1.25 – 4.09) compared with ND cases, but there were no significant differences between CC and PC cases (Table 2). Of those reporting ≥1 new ReA symptom on the AReA questionnaire, 45 (75.0%) CC, 13 (68.4%) PC, and 14 (82.4%) ND cases completed the rheumatologist telephone interview (Figure 1). Non-participation at each stage of surveys was due to inability to contact participants after three attempts. Nineteen CC cases met the probable ReA case definition. Assuming no other cases occurred in the eligible population (N=224), then a minimum of 8.5% of CC cases experienced ReA. Similarly, 4 (2.8%) of 144 PC and 2 (0.6%) of 329 ND cases met the probable ReA case definition. Assuming persons

reporting new ReA symptoms on the screening questionnaire who did not complete the rheumatologist interview experienced ReA at the same rate as those interviewed, an estimated maximum of 23.9% of CC cases, 12.4% of PC cases, and 2.15% of ND cases who completed the screening questionnaire developed probable ReA (Table 2). Calculation can be referenced in Supplementary Appendix 3). The maximum ReA rates were higher among CC (RR 11.4; 95% CI: 3.13 – 41.2) and PC cases (RR 4.87; 95% CI: 1.09 – 21.8) than ND cases. There was no significant difference in maximum ReA rates between CC and PC cases.

No probable ReA cases were identified in children (aged ≤18 years) among PC and ND cases. Of CC cases, adults were not at higher risk for probable ReA compared with children (RR 1.18; 95% CI: 0.464–3.02). There was no sex predominance for probable ReA cases compared with those who did not develop ReA, even when comparing within outbreak case types. Probable ReA cases reported gastroenteritis duration lasted twice as long compared with those who did not develop ReA (median 14 vs 7 days; p<0.001). There were insufficient responses to calculate the median interval between onset of gastroenteritis and development of ReA.

Based on the rheumatologist interview, joint symptoms were the most common initial symptom in probable ReA cases. All PC and ND ReA cases and 95% of CC ReA cases developed either joint pain or swelling during the course of their disease (Table 3). Ankle (48%), knee (40%), and feet (28%) were the most common joints involved across outbreak case types. Other than eye symptoms (32%), extra-articular symptoms were uncommon. Three CC cases requiring hospitalization for severe gastroenteritis developed probable ReA. In addition, two probable ReA cases reported receiving a specialist physician diagnosis of ReA to the study rheumatologist.

DISCUSSION

We report probable ReA occurring in 8.5–23.9% of CC and 2.15–12.4% of PC cases in a large waterborne *Campylobacter* gastroenteritis outbreak in Havelock North, New Zealand caused by ovine faecal contamination of the untreated reticulated ground water system following a heavy rainfall event.[16] ReA incidence estimates following *Campylobacter* infections vary widely. One meta-analysis reported incidences from 0-24% with a summary estimate of 2.9%.[6] Larger surveillance platforms generally estimate lower ReA incidence, likely due less reporting of gastroenteritis cases to primary care than occurs in an outbreak setting where disease reporting is often enhanced.[6] Additionally, prolonged latency between gastroenteritis onset and investigation for ReA often resulted in lower ReA incidence estimates. Achieving accurate ReA estimates is challenging in population-based studies using healthcare databases because there is insufficient standardization of ICD-10 coding for ReA and inconsistent recording of related codes.[8] Outbreak-based studies have the benefit of following a similarly exposed cohort to determine ReA incidence. However, many studies prospectively follow notified gastroenteritis cases of which few are culture-confirmed,[3, 11-13] weakening associations between ReA incidences and the suspected pathogen. Furthermore, some uncultured infections in these studies could be caused by pathogens not known to precipitate ReA, further diluting the ReA incidence estimates.[8, 12, 13] Other outbreak-based studies only investigate culture-confirmed cases.[13-15] In doing this, they limit the description of ReA to affected individuals who sought medical care.

Our study design has the advantage of addressing a number of these issues by comparing three case types typically encountered in an outbreak: culture-confirmed gastroenteritis, self-reported gastroenteritis, and those exposed who do not develop diarrhoea. We found probable ReA was

more common among CC and PC cases compared with ND cases with no difference in rates between CC and PC cases. Though small PC sample size may have precluded detection of differences between CC and PC cases. Garg *et al*. investigated similar diarrhoeal presentations, including asymptomatic, self-reported gastroenteritis, and gastroenteritis presenting to medical care and found higher incidences than we report; however, their outcome of interest was new arthritis, not specifically defined as ReA.[7] They only report significant differences between medical care-seeking cases and asymptomatic cases. The trend towards higher probable ReA rates among CC cases may be associated with longer gastroenteritis duration, which may have increased the likelihood of seeking medical care and having the illness confirmed by faecal culture.

A unique feature of our study is the inclusion of rheumatologist telephone interview to confirm joint and extra-articular symptoms, leading to more refined ReA incidence estimates. Rheumatologist review is more commonly seen in population-based studies,[1, 4, 18, 19] which may be due to more available resources and less time constraints compared with outbreak-based studies. However, we demonstrate with a retention rate of 68–82% for rheumatologist telephone interview that this is a feasible method for the outbreak setting. This retention rate is substantially higher than other outbreak studies using rheumatologist examination as the sole means to estimate ReA incidence,[3, 11] and timelier than others with high rheumatologist review rates,[15] likely improving the precision of our incidence estimates. Additionally, our approach is a less resource- and labour-intensive method than those requiring rheumatologist physical examination, making it a distinct and viable option for investigating ReA in future outbreaks.

ND cases may represent asymptomatic *Campylobacter* infections as opposed to uninfected residents,[7, 12, 20] but case status remains unclear since no faecal specimens were tested in this population and some ND cases reported mild, non-diarrhoeal gastrointestinal symptoms. Multiple studies have shown that culture-confirmed infections can present without diarrhoea[21, 22] or can be asymptomatic in up to 15% of cases.[23-26] In fact, findings from one outbreak demonstrated that asymptomatic individuals exposed to a contaminated water supply developed more joint symptoms than an unexposed population.[20] Others have reported 8–10% of asymptomatic individuals who consumed contaminated food during Salmonella outbreaks developed ReA.[9, 27] Although ND cases may represent outbreak-related infections, our results are consistent with previous findings that individuals without diarrhoea are at lower risk for developing ReA compared with those who experience diarrhoea.[20, 27]

Although PC and ND cases were more likely to be older and female, we found no sex or age differences in the probable ReA cases compared with those who did not develop ReA. This is in contrast with recent studies reporting a predominance of females[1, 4, 11, 19] and higher ReA incidence among adults compared with children;[1, 12] Most probable ReA cases presented with mild symptoms and few sought medical care, consistent with previous *Campylobacter* outbreaks.[4, 11, 13] As with previous studies, knee and ankle were the sites most commonly involved[1-3, 13] and extra-articular manifestations were rare.[11] Data on the association between gastroenteritis severity and development of ReA are conflicting. Probable ReA cases had longer duration than those without ReA. Similarly, many have shown higher severity[1, 2] and longer duration of gastroenteritis[4, 9, 12, 27] associated with higher risk of ReA development, whereas others have shown no association.[2, 4, 13, 14]

This study had several limitations. Post-outbreak whole genome sequencing revealed that outbreak-related campylobacteriosis cases likely had onset dates between August 7 – 24 [16]. Given limitations in our enrolment design, we were unable to amend our outbreak period. This would have little impact on ReA rates attributed to CC cases because each is culture-confirmed campylobacteriosis; however, inclusion of PC cases beyond the true outbreak period may have over attributed diarrheal cases to campylobacteriosis in 22 PC cases, including 2 cases with probable ReA. Our screening phone survey response rates were not as high as some studies using similar methods,[9, 12] and use of a landline sampling frame may have reduced recruitment of younger and economically-deprived households. These biases as well as willingness to participate could impact the comparison of minimum ReA rates between groups, so we chose to compare maximum ReA rates because this analysis would be primarily limited by participation bias.

Cases were not examined by a rheumatologist and classification of joint involvement was dependent on a patient's self-report, preventing definitive diagnosis of ReA. It is possible that individuals seeking medical care, such as CC cases, were more likely to report medical conditions and symptoms, including ReA symptoms. In the absence of physical examination by a rheumatologist, this bias could contribute to the trend towards higher ReA incidence seen in this population.[7] Furthermore, these individuals may be more likely to report more gastroenteritis symptoms during the survey, potentially biasing the association between gastroenteritis severity and ReA development.[19]

Given resource limitations, we were unable to perform follow-up assessments of existing cases to assess disease remission and chronicity. Although the timeliness of our survey likely reduced recall bias compared with other studies,[9, 15] it also prohibited identification of incident cases

occurring greater than 12 weeks following the outbreak. Ternhag *et al.* demonstrated that initial ReA surveillance identified few cases at 3 months, but follow-up 1 year revealed new, associated cases.[17] Also, although we compared CC and PC cases with ND cases, we did not have the resources to study an unexposed, control group. As such, we have no ReA baseline incidence with which to compare our rates.[20]

Our findings have several important implications. They underscore the importance of advising populations affected by *Campylobacter* outbreaks that delayed effects can occur. These individuals and doctors should be alerted to the risk of ReA following *Campylobacter* outbreaks. As ReA impacts short- and long-term health outcomes, outbreak-associated economic assessments should consider including costing for this sequela.[28]

In summary, we present a high probable ReA incidence among a spectrum of gastroenteritis case types during a very large *Campylobacter* gastroenteritis outbreak, providing a comprehensive characterisation of ReA in an exposed population. We describe a screening survey and rheumatologist review method that provides a more refined approach than use of a screening questionnaire alone. This method serves as a practical and resource-efficient alternative to in-person rheumatologic exams and is a feasible option for estimation of ReA burden in future gastroenteritis outbreaks.

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Competing Interests. Authors have no financial or personal relationships with people or organisations that could inappropriately bias their work.

Data Availability. The data underlying this article are available in the article and in its online supplementary material.

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Contributorship and Guarantorship Statement

Tiffany Walker- Led surveillance, assisted with study design, conducted analysis, performed literature review, drafted manuscript. Dr. Walker serves as the guarantor.

Rebecca Grainger- Assisted with literature review, assisted with study design, conducted rheumatologic interviews, assisted with interpretation of findings, reviewed manuscript.

Terry Quirke- Assisted with study design, assisted with data analysis, assisted with interpretation of findings, reviewed manuscript.

Rebekah Roos- Assisted with literature review, assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Jill Sherwood- Assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Graham Mackereth- Conducted household survey, assisted with study design, assisted with data analysis, assisted with interpretation of findings, reviewed manuscript.

Tomasz Kiedrzynski- Assisted with household study design, assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Shevaun Paine- Assisted with household study design, assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Tim Wood- Assisted with household study design, assisted with interpretation of findings, reviewed manuscript.

Anita Jagroop- Assisted with interpretation of findings, reviewed manuscript.

Michael G. Baker- Assisted with interpretation of findings, reviewed manuscript.

Nicholas Jones- Provided project oversight, assisted with interpretation of findings, reviewed manuscript.

References

1. Townes JM, Deodhar DA, Swanson E, Smith K, Krug HE, Barkhuizen A, et al. Reactive arthritis following culture-confirmed infections with bacterial enteric pathogens in Minnesota and Oregon: A population-based study. *Annals of Rheumatic Diseases* 2008;67(12):1689–96.
2. Schönberg-Norio D, Mattila L, Lauhio A, et al. Patient-reported complications associated with Campylobacter jejuni infection. *Epidemiol Infect* 2010;138(7):1004–11.
3. Hannu T, Kauppi M, Tuomala M, et al. Reactive arthritis following an outbreak of Campylobacter jejuni infection. *J Rheumatol* 2004;31(3):528–30.
4. Hannu T, Mattila L, Rautelin H, et al. Campylobacter-triggered reactive arthritis: a population-based study. *Rheumatology* 2002;41(3):312–18.
5. Ajene AN, Fischer Walker CL, Black RE. Enteric pathogens and reactive arthritis: a systematic review of Campylobacter, salmonella and Shigella-associated reactive arthritis. *J Health Popul Nutr* 2013;31(3):299–307.
6. Keithlin J, Sargeant J, Thomas MK, et al. Systematic review and meta-analysis of the proportion of Campylobacter cases that develop chronic sequelae. *BMC Public Health* 2014;14:1203.
7. Garg AX, Pope JE, Thiessen-Philbrook H, et al. Arthritis risk after acute bacterial gastroenteritis. *Rheumatology* 2008;47(2):200–04.
8. Curry JA, Riddle MS, Gormley RP, et al. The epidemiology of infectious gastroenteritis related reactive arthritis in U.S. military personnel: a case-control study. *BMC Infectious Diseases*.2010;10:266.
9. Locht H, Krogfelt K. Comparison of rheumatological and gastrointestinal symptoms after infection with Campylobacter jejuni/coli and enterotoxigenic Escherichia coli. *Annals of the Rheumatic Diseases* 2002;61(5):448–52.

10. Buxton JA, Fyfe M, Berger S, et al. Multiprovincial Salmonella typhimurium Case-Control Study Group. Reactive arthritis and other sequelae following sporadic Salmonella typhimurium infection in British Columbia, Canada: a case control study. *J Rheumatol* 2002;29(10):2154–58.
11. Uotila T, Antonen J, Laine J, et al. Reactive arthritis in a population exposed to an extensive waterborne gastroenteritis outbreak after sewage contamination in Pirkanmaa, Finland. *Scand J Rheumatol* 2011;40(5):358–62.
12. Arnedo-Pena A, Beltrán-Fabregat J, Vila-Pastor B, et al. Reactive arthritis and other musculoskeletal sequelae following an outbreak of Salmonella hadar in Castellon, Spain. *J Rheumatol* 2010;37(8):1735–42.
13. Locht H, Mølbak K, Krogfelt KA. High frequency of reactive joint symptoms after an outbreak of Salmonella enteritidis. *J Rheumatol* 2002;29(4):767–71.
14. Rohekar S, Tsui FW, Tsui HW, et al. Symptomatic acute reactive arthritis after an outbreak of salmonella. *J Rheumatol* 2008;35(8):1599–602.
15. Lee AT, Hall RG, Pile KD. Reactive joint symptoms following an outbreak of Salmonella typhimurium phage type 135a. *J Rheumatol* 2005;32(3):524–27.
16. Gilpin BJ, Walker T, Paine S, et al. A large scale waterborne Campylobacteriosis outbreak, Havelock North, New Zealand [published online ahead of print, 2020 Jun 29]. *J Infect*. 2020;S0163-4453(20)30445-X.
17. Ternhag A, Törner A, Svensson Å, et al. Short- and Long-term Effects of Bacterial Gastrointestinal Infections. *Emerging Infectious Diseases* 2008;14(1):143–48.
18. Hannu T, Mattila L, Siitonen A, et al. Reactive arthritis attributable to Shigella infection: a clinical and epidemiological nationwide study. *Annals of the Rheumatic Diseases* 2005;64(4):594–98.

19. Schiellerup P, Krogfelt KA, Locht H. A comparison of self-reported joint symptoms following infection with different enteric pathogens: effect of HLA-B27. *J Rheumatol* 2008;35(3):480–87.

20. Laine J, Uotila T, Antonen J, et al. Joint symptoms after a large waterborne gastroenteritis outbreak—a controlled, population-based questionnaire study. *Rheumatology 2012*;51(3):513–18.

21. Amour C, Gratz J, Mduma E, et al. Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) Network Investigators. Epidemiology and Impact of Campylobacter Infection in Children in 8 Low-Resource Settings: Results From the MAL-ED Study. *Clin Infect Dis* 2016;63(9):1171–79.

22. Mason J, Iturriza-Gomara M, O'Brien SJ, et al. Campylobacter Infection in Children in Malawi Is Common and Is Frequently Associated with Enteric Virus Co-Infections. *PLoS ONE* 2013;8(3):e59663.

23. Komba EV, Mdegela RH, Msoffe PL, et al. Prevalence, Antimicrobial Resistance and Risk Factors for Thermophilic Campylobacter Infections in Symptomatic and Asymptomatic Humans in Tanzania. *Zoonoses Public Health* 2015;62(7):557–68.

24. Lääveri T, Antikainen J, Pakkanen SH, et al. Prospective study of pathogens in asymptomatic travellers and those with diarrhoea: aetiological agents revisited. *Clin Microbiol Infect* 2016;22(6):535–41.

25. Lindblom GB, Ahrén C, Changalucha J, et al. Campylobacter jejuni/coli and enterotoxigenic Escherichia coli (ETEC) in faeces from children and adults in Tanzania. *Scand J Infect Dis* 1995;27(6):589–93.

26. Zaidi MB, McDermott PF, Campos FD, et al. Antimicrobial-resistant Campylobacter in the food chain in Mexico. *Foodborne Pathog Dis* 2012;9(9):841–47.

27. Dworkin MS, Shoemaker PC, Goldoft MJ, et al. Reactive arthritis and Reiter's syndrome following an outbreak of gastroenteritis caused by Salmonella enteritidis. *Clin Infect Dis* 2001;33(7):1010–14.

28. Moore D, Drew R, Davies P, et al. The Economic Costs of the Havelock North August 2016 Waterborne Disease Outbreak, Report prepared for the Ministry of Health. Sapere Research Group Ltd., Wellington, NZ. September 2020. https://www.health.govt.nz/publication/economic-costs-havelock-north-august-2016-waterborne-disease-outbreak. Accessed 5/2020.

Table 1. Demographic and clinical characteristics of reactive arthritis (ReA) surveillance enrolees and probable ReA cases by outbreak case type

	All ReA surveillance enrolees				Probable ReA cases		
Participant characteristics	**CC* (N=106)**	**PC* (N=47)**	**ND* (N=113)**	**p-value**	**CC* (N=19)**	**PC* (N=4)**	**ND* (N=2)**
Female	48 (45%)	31 (66%)	74 (65%)	<0.001	8 (42%)	2 (50%)	2 (100%)
Age, median (range)	47 (1–96)	55 (15–85)	62 (16–99)	<0.001	43 (10–73)	69 (54–78)	68 (49–86)
≤18 years	28 (26%)	1 (2%)	1 (1%)		5 (26%)	0	0
>18 years	78 (74%)	46 (98%)	112 (99%)		14 (74%)	4 (100%)	2 (100%)
Race/Ethnicity				<0.001			
Maori	7 (7%)	2 (4%)	0		1 (5%)	0	0
Pacific Islander	2 (%)	0	0		1 (5%)	0	0
NZ European	85 (80%)	38 (81%)	97 (86%)		17 (89%)	4 (100%)	1 (50%)
Other European	8 (8%)	6 (13%)	16 (14%)		0	0	1 (50%)
Asian	3 (3%)	1 (2%)	0		0	0	0
Other	1(1%)	0	0		0	0	0
Gastroenteritis symptoms[¥]				<0.001			
0	13 (12%)	8 (17%)	101 (89%)		1 (5%)	2 (50%)	0
1	14 (13%)	10 (21%)	6 (5%)		0	1 (25%)	0
2	17 (16%)	15 (32%)	3 (3%)		2 (11%)	1 (25%)	2 (100%)
3	39 (37%)	9 (19%)	3 (3%)		7 (37%)	0	0
4	23 (22%)	5 (11%)	0		9 (47%)	0	0
Gastroenteritis duration, median (range) [γ]	10 (2–62)	7 (1–31)	3 (1–17)	0.0014	14 (3–62)	10 (4–28)	2 (2)

*CC: confirmed campylobacteriosis case; PC: probable campylobacteriosis case; ND: No diarrhoea case

[¥]Includes fever, nausea, vomiting, abdominal pain

[γ]missing gastroenteritis duration for 5 confirmed campylobacter and 1 probable campylobacter case from all ReA enrolees; missing gastroenteritis duration for 1 probable and 1 no diarrhoea probable ReA case

Table 2. New ReA symptom and probable reactive arthritis (pReA) incidence among outbreak case types following Havelock North *Campylobacter* gastroenteritis outbreak

Case Type	≥1 New ReA symptom	RR (95% CI)*¥	RR (95% CI)ɣ	Maximum pReA Rate	RR (95% CI)*¥	RR (95% CI)ɣ
CC	56.6%	3.76 (2.35–6.01)	1.40 (0.95–2.06)	23.9%	11.4 (3.13– 41.2)	2.22 (0.90–5.43)
PC	40.4%	2.26 (1.25–4.09)		12.4%	4.87 (1.09 – 21.8)	
ND	15.0%			2.15%		

*RR: relative risk; CI: confidence interval; CC: confirmed campylobacteriosis case; PC: probable campylobacteriosis case; ND: No diarrhoea case

¥compared with no diarrhoea cases

ɣcompared with probable campylobacteriosis cases

Table 3. Clinical characteristics among probable reactive arthritis (ReA) cases by outbreak case type

Rheumatologic symptoms	CC* (N=19)	PC* (N=4)	ND* (N=2)	All probable ReA (N=25)
Initial symptom				
Joint	15 (79%)	4 (100%)	2 (100%)	21 (84%)
Eye	1 (7%)	0	0	1 (4%)
Oral	1 (7%)	0	0	1 (4%)
Joint symptoms				
Pain	18 (95%)	4 (100%)	2 (100%)	24 (96%)
Swelling	8 (42%)	2 (50%)	2 (100%)	11 (44%)
Pain or Swelling	18 (95%)	4 (100%)	2 (100%)	24 (96%)
Number of swollen joints¥				
0	11 (58%)	2 (50%)	0	7 (28%)
1	2 (11%)	1 (25%)	1 (50%)	4 (16%)
2	3 (16%)	0	0	5 (20%)
3	0	1 (25%)	0	4 (16%)
4	1 (5%)	0	0	1 (4%)
5	0	0	0	0
6	0	0	1 (50%)	1 (4%)
Joint sites**				
Hand	4 (21%)	1 (25%)	0	5 (20%)
Wrist	3 (16%)	1 (25%)	0	4 (25%)
Elbow	4 (21%)	1 (25%)	0	5 (20%)
Shoulder	2 (11%)	1 (25%)	0	3 (12%)
Feet	5 (26%)	1 (25%)	1 (50%)	7 (28%)
Ankle	10 (53%)	0	2 (100%)	12 (48%)
Knee	6 (32%)	3 (75%)	1 (50%)	10 (40%)
Hip	5 (26%)	0	1 (50%)	6 (24%)
Back	4 (21%)	1 (25%)	1 (50%)	6 (24%)
Extra-articular symptoms				
Heel	2 (11%)	1 (25%)	0	3 (12%)

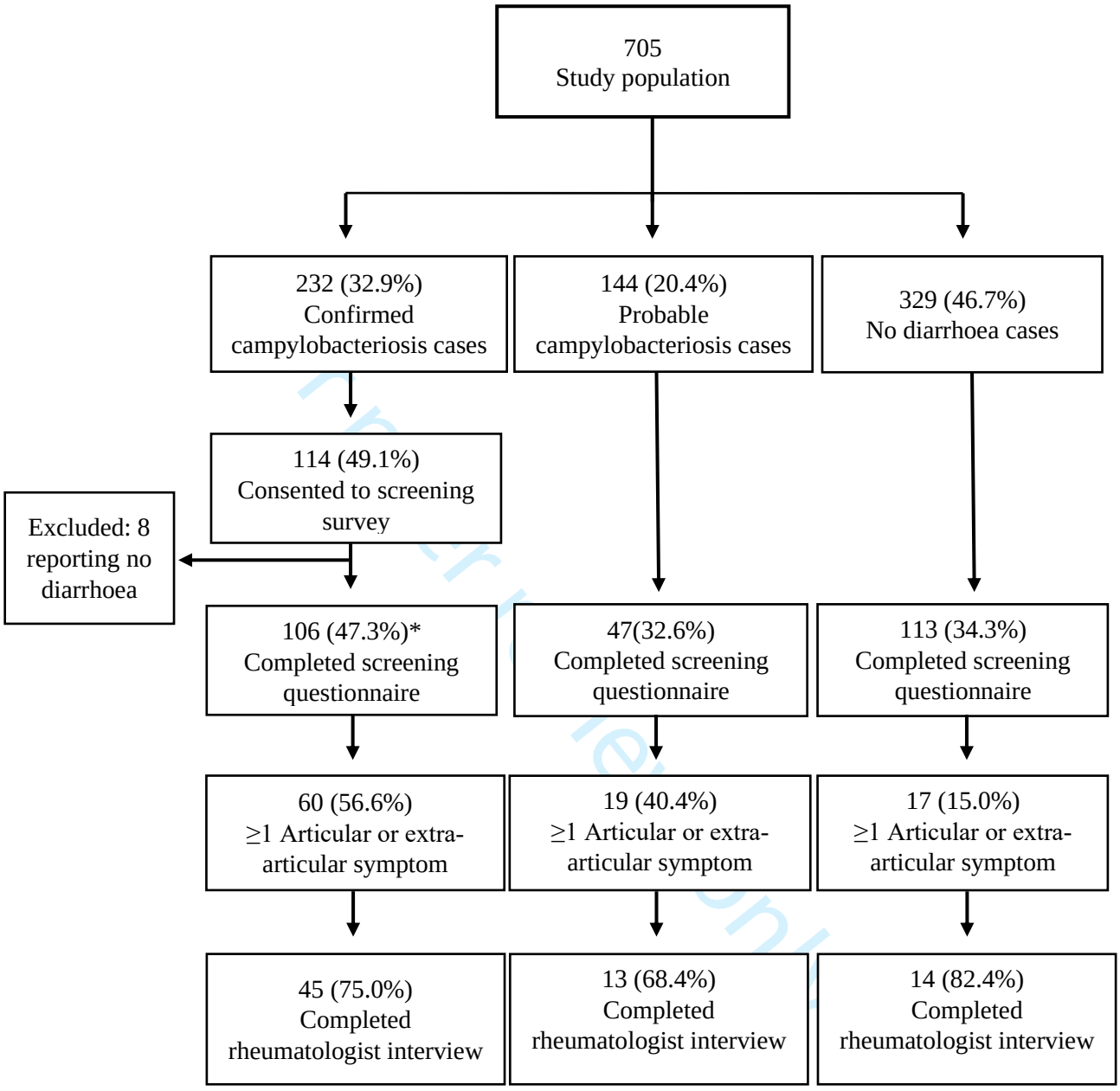
Other tendon	1 (5%)	0	1 (50%)	2 (8%)
Mouth ulcers	4 (21%)	0	0	4 (16%)
Sore eyes	6 (32%)	0	2 (100%)	8 (32%)
Conjunctivitis	3 (16%)	0	1 (50%)	4 (16%)
Morning stiffness	13 (68%)	4 (100%)	1 (50%)	18 (72%)
<1 hour	9	3	1	13 (52%)
≥ 1 hour	4	1	0	5 (20%)

*CC: confirmed campylobacteriosis case; PC: probable campylobacteriosis case; ND: No diarrhoea case

¥ missing number of joints affected in two CC cases reporting joint swelling

**Includes joint pain or swelling

Figure 1. Reactive arthritis (ReA) surveillance following Havelock North *Campylobacter* gastroenteritis outbreak: Screening questionnaire and rheumatologist interview enrolment



*Percent calculated from confirmed campylobacteriosis cases reporting diarrhoea (N=224)

Supplementary Appendix 1. Adapted AReA Telephone Screening Questionnaire

1. Were you exposed to the Havelock North reticulated water supply [including drinking water or using water to prepare food] from 5th to 12th August 2016?

□ Yes □ No [If No, no further information is required].

2. Did you experience any of the following symptoms between 5th August and 6th September?

□ Diarrhoea □ Vomiting □ Abdominal Pain □ Fever (38C) □ Nausea □ None

3. If you had symptoms, what was the first date you had diarrhoea, vomiting, abdominal pain, nausea or fever related to your infection? _____

4. If you had symptoms, what was the duration of your illness? _____ (days)

6. If you had symptoms, were you prescribed antibiotics for the illness? □ Yes □ No

If yes, what antibiotics?_____

For the rest of the survey, I would like to ask you about symptoms that you may have had since the outbreak started that may indicate whether you had a condition called Reactive Arthritis. This is a disease that can occur after a diarrhoeal illness and is not limited to joint pains. If you had diarrhoea, I am asking about symptoms that occurred AFTER you were sick with diarrhoea.

Since the start of the outbreak, have you experienced ANY of the following symptoms for 3 consecutive DAYS or more?

7. Joint pain, swelling or stiffness?	Yes	No
8. Visibly swollen joints?	Yes	No
9. Swollen joints which could not be straightened out?	Yes	No
10. Stiffness in the joints for half hour or m	Yes	No
11. Heel pain?	Yes	No
12. Red, itchy, or burning eyes?	Yes	No
13. Painful mouth ulcers?	Yes	No
14. Rash on genitals?	Yes	No
15. Discharge from genitals or burning on urination?	Yes	No

16. Rash on palms or soles/	Yes	No

17. What was the first date these symptoms started? (If you had diarrhoea, this would be the first date you noticed these symptoms AFTER your diarrhoea started)_____(dd/mm/yy)

18. Information from this survey will be reviewed by a medical specialist to determine whether your symptoms are concerning for reactive arthritis. If so, you are eligible to be recontacted by telephone to be interviewed by the medical specialist. She will ask you additional questions about your symptoms to confirm or rule out the diagnosis of reactive arthritis. Would you be willing to participate in the follow-up interview if you meet the criteria? □ Yes □ No

Supplementary 2. Rheumatologist Telephone Interview Questionnaire

Details of suspected Reactive arthritis and related extra-articular features

1. What was the first symptom? (please circle): joint / oral / eye / genital / skin
2. What was the date of their first new symptom? _____

Musculoskeletal features:

3. Has the patient experienced joint pain? □ Yes □ No
4. Have any joints been swollen? □ Yes □ No
5. How many joints were swollen? _____
6. Which areas were painful or swollen (please tick):

SITE	INVOLVED (Y/N)	PAIN (Y/N)	SWELLING (Y/N/NA)	SIDE (R/L/B/NA)	SEQUENCE (1^{ST}, 2^{ND}, ALL, NA)	DURATION (DAYS)	RESOLVED (Y/N)
Hands							
Wrists							
Elbow							
Shoulder							
Feet							
Heel							
Ankle							
Knee							
Hip							
Back							
Tendons							

7. Has the person experienced MORNING joint stiffness? □ Yes □ No

   7 b. If yes, please indicate duration of MORNING joint stiffness_____ (minutes/hours/all day)

8. Has the person had painful tendon insertion sites? □ Yes □ No
   8b. If yes please state sites/s_____

Oral features:

9. Has the person had any mouth ulcers? □ Yes □ No

Eye features:

10. Has the person had:
    a. Sore eyes? □ Yes □ No
    b. Conjunctivitis? □ Yes □ No
    c. Uveitis? □ Yes □ No

Genital features:

11. Has the person had:
    a. Urinary symptoms? □ Yes □ No
    b. Urethritis □ Yes □ No
    c. Circinate balanitis? □ Yes □ No

Skin features:

12. Has the person had:
    a. New skin rash of palms of hands? □ Yes □ No
    b. New skin rash of soles of feet? □ Yes □ No
13. Keratoderma blennorrhagia? □ Yes □ No
14. Other_____

Supplementary Appendix 3. Calculation of Maximum Probable ReA Rate

[[(Rate of probable ReA)*(Participants with ≥1 ReA symptom who did not participate in Rheumatologist interview)] + Probable ReA cases]/Enrollees in AReA screening survey

CC: [[(19/45)*(60-45)] +19]/106

PC: [[(4/13)*(19-13)] +4]/47

ND: [[(2/14)*(17-14)] +2]/113

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/a
		(*e*) Describe any sensitivity analyses	N/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8, Table 1, 3
Outcome data	15*	Report numbers of outcome events or summary measures	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Reactive Arthritis Incidence in a Community Cohort following a Large Waterborne Campylobacteriosis Outbreak in Havelock North, New Zealand

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Abstract

Objectives

In August 2016, *Campylobacter* spp. contaminated an untreated reticulated water supply resulting in a large-scale gastroenteritis outbreak affecting an estimated 8,320 people. We aimed to determine the incidence of probable reactive arthritis (ReA) cases in individuals with culture-confirmed campylobacteriosis (CC), self-reported probable campylobacteriosis (PC), and those reporting no diarrhea (ND).

Design

We conducted a retrospective cohort study to identify incidence of probable ReA cases. We identified cases with new ReA symptoms using an adapted Acute Reactive Arthritis (AReA) telephone questionnaire. Those reporting ≥1 symptom underwent a telephone interview with the study rheumatologist. Probable ReA was defined as spontaneous onset of pain suggestive of inflammatory arthritis in ≥ 1 previously asymptomatic joint for ≥ 3 days occurring ≤ 12 weeks after outbreak onset.

Setting

Population-based epidemiologic study in Havelock North, New Zealand

Participants

We enrolled notified CC cases with gastroenteritis symptom onsets 5 August – 6 September 2016 and conducted a telephone survey of households supplied by the contaminated water source to enrol PC and ND cases.

Results

One hundred and six (47.3%) CC, 47 (32.6%) PC, and 113 (34.3%) ND cases completed the AReA telephone questionnaire. Of those reporting ≥1 new ReA symptom, 45 (75.0%) CC, 13 (68.4%) PC, and 14 (82.4%) ND cases completed the rheumatologist telephone interview. Nineteen CC, 4 PC, and 2 ND cases developed probable ReA, resulting in minimum incidences of 8.5%, 2.8%, and 0.6% and maximum incidences of 23.9%, 12.4%, and 2.15%.

Discussion

We describe high probable ReA incidences among gastroenteritis case types during a very large *Campylobacter* gastroenteritis outbreak using a resource-efficient method that is feasible to employ in future outbreaks.

Keywords: Reactive arthritis, epidemiology, infections

Strengths and Limitations of this study

Strengths

- Reported Campylobacteria-associated ReA rates vary due to different methodologic approaches that limit inclusion to one gastroenteritis type (self-reported versus culture-proven).
- To address these limitations, we estimated the incidence and characterized the clinical presentations of probable ReA cases in three groups: individuals with culture-confirmed campylobacteriosis, those with self-reported gastroenteritis, and those reporting no diarrhoea during a large campylobacteriosis outbreak
- We offer a comprehensive description of ReA rates based on gastroenteritis severity to guide practitioners.

Limitations

- Cases were not examined by a rheumatologist; classification of joint involvement was dependent on a patient's self-report, preventing definitive diagnosis of ReA

INTRODUCTION

Reactive arthritis (ReA) is a known post-infectious sequelae of *Campylobacter* gastroenteritis with a clinical spectrum ranging from transient arthralgias to severe peripheral and/or axial arthritis with occasional extra-articular features.[1, 2] Estimates of ReA incidence following *Campylobacter* infection vary widely from 1–26%.[2-7] This wide variation is likely due, in part, to lack of a standard definition for ReA and varying methods for estimating ReA incidence.[6] Population-based studies have estimated ReA incidence by sampling individuals with culture-proven bacterial gastroenteritis;[1, 2, 4] however, it is estimated that less than a quarter of gastroenteritis cases seek medical consultation and only 50% of those have a faecal specimen cultured.[8] This method likely underestimates ReA incidence. Furthermore, there is often a delay between gastroenteritis development and investigation for ReA,[9, 10] which may reduce capture of ReA cases.

Outbreak-based studies allow estimation of ReA incidence in a cohort of exposed individuals; however, many studies use self-reported gastroenteritis because culture confirmation can exceed laboratory capacity during a large outbreak.[3, 11-13] Some outbreak-based studies have calculated ReA incidence exclusively in culture-positive gastroenteritis cases.[14, 15] Both approaches typically rely on data from exposed individuals who sought medical care, excluding cases with less severe presentations, and thereby limiting not only ReA incidence estimates, but potentially narrowing the described clinical spectrum of ReA in the affected population.

During 5–12 August 2016, the untreated reticulated water supply to Havelock North, New Zealand became contaminated with sheep faecal matter following a heavy rainfall event. This resulted in a narrow exposure outbreak of *Campylobacter spp*. gastrointestinal infections,

affecting an up to 8,320 people. [16] To address the above-mentioned limitations of previous ReA epidemiologic studies, we aimed to estimate the incidence and characterize the clinical presentations of probable ReA cases in three groups; individuals with culture-confirmed campylobacteriosis, those with self-reported probable gastroenteritis, and those reporting no diarrhoea during the outbreak period.

METHODS

Cohort Description

The Hawke's Bay District Health Board (HBDHB) provides medical care and public health services for approximately 164,000 people in a 14,000 square kilometre area, including metropolitan and rural populations. The catchment area includes Havelock North, which has a population of 14,118 and its own reticulated drinking water derived from untreated ground water. Prospective, population-based surveillance for acute gastrointestinal illnesses was conducted among residents of the HBDHB catchment area during 13 August – 6 September 2016, and faecal specimens were submitted to local laboratories for culture.[16] Additionally, we conducted active surveillance through four rounds of telephone survey. We randomly sampled the same panel of 250 Havelock North households supplied by the contaminated municipal water source. The last survey occurring 7 weeks following the outbreak onset to identify additional gastroenteritis infections among residents who did not seek healthcare as well as identify exposed individuals who did not develop diarrhoea.

Patient and public involvement

Local community leaders were consulted in the design of this study to ensure outcomes met the priorities of the community. Preliminary communication about this study were distributed by the local media to the public to inform the population of the impact of this outbreak.

Campylobacter gastroenteritis outbreak case definitions

The study population included three groups. A confirmed campylobacteriosis (CC) case was defined as an individual who consumed reticulated water from Havelock North, New Zealand from 5 – 12 August 2016 with clinician-confirmed diarrhoea between 5 August – 6 September 2016 with a positive faecal specimen for *Campylobacter* spp. A probable campylobacteriosis (PC) case was defined as an individual from the household telephone survey with the same exposure as a CC case who developed diarrhoea between 5 August – 6 September 2016 without presentation to healthcare or provision of faecal specimen. No diarrhoea participants (ND cases) were also identified by the household telephone survey and had the same exposure to contaminated water as a PC case but did not develop diarrhoea between 5 August – 6 September 2016. Seven weeks after the outbreak onset, all eligible cases were contacted by telephone to consent for enrolment into ReA surveillance.

ReA screening questionnaire and rheumatologist interview

Using an adapted version of the previously validated Acute Reactive Arthritis (AReA) questionnaire,[14] (Supplementary Appendix 1) we administered a ten-question telephone survey through a commercial survey provider to ReA surveillance enrolees eight weeks after the outbreak onset. To comply with case definitions, we excluded 7 CC cases from the survey who denied a history of diarrhoea during the outbreak. All ages were included; parents or guardians provided proxy responses for children aged <15 years. Approximately 12 weeks after outbreak onset, respondees reporting ≥1 symptom on the AReA questionnaire underwent a telephone interview with the study rheumatologist, RG, who has 15 years' experience in rheumatology practice. Participants were asked about the inflammatory nature and onset of joint symptoms. (Supplementary Appendix 2). The study rheumatologist defined a probable ReA case as spontaneous onset of pain suggestive of inflammatory arthritis in ≥ 1 previously

asymptomatic joint for ≥ 3 consecutive days occurring ≤ 12 weeks after outbreak onset in a CC, PC, or ND cases.

Ethics

New Zealand Health and Disabilities Ethics Committee approval was obtained prior to study enrolment.

Data analysis

Differences in baseline characteristics between outbreak case types were assessed using chi-square or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. Minimum ReA rates are reported as the proportion of probable ReA cases occurring out of the total number of residents eligible for enrolment for each outbreak case type. Maximum ReA rates were estimated by applying the proportion of probable ReA cases occurring in residents who reported ≥1 ReA symptoms on the screening survey that completed the rheumatologist interview to those who reported ≥1 ReA symptoms but failed to complete the rheumatologist interview, then dividing the sum by the population that completed the screening survey. This was calculated for each outbreak case type individually. Relative risk (RR) and 95% confidence intervals (CI) were calculated to assess the risk of developing probable ReA among outbreak case types and among adults compared with children. P-values ≤0.05 were considered significant. Data were analysed using SAS 9.4.

RESULTS

A total of 232 CC cases were notified to HBDHB. Of these, 114 (49.1%) participated in the AReA screening telephone questionnaire at 8 weeks; however, 8 responders reported no history of diarrhoea and were excluded from the remainder of the questionnaire, leaving 106 (47.3%)

of 224 eligible CC cases completing the AReA questionnaire (Figure 1). A total of 144 PC and 329 ND cases were identified from the randomly sampled household survey of which 47 (32.6%) PC and 113 (34.3%) ND cases completed the AReA questionnaire. Forty-three (40.6%) CC, 16 (34.0%) PC, and 11 (9.73%) ND cases reported new joint symptoms after outbreak onset. New extra-articular symptoms including heel pain, eye symptoms, mouth ulcers, genital rash or discharge, or palm or sole rash were reported by 42 (39.6%) CC, 12 (25.5%) PC, and 12 (10.6%) ND cases.

PC and ND cases were older ($p<0.001$) and more likely to be female ($p<0.001$) compared with CC cases (Table 1). CC cases were more likely to be of Maori or Pacific ethnicities than PC and ND cases ($p<0.01$). CC cases had longer duration of gastroenteritis symptoms (fever, nausea, vomiting, abdominal pain) (median= 10 days) compared with PC (median=7 days) and ND cases (median=3 days) ($p=0.0014$). More CC cases had new joint ($p<0.001$) and extra-articular symptoms ($p<0.001$) compared with ND cases. There were no differences between CC and PC cases for joint or extra-articular symptoms.

The rate of new ReA symptoms was higher among CC (RR 3.76; 95% CI: 2.35 – 6.01) and PC cases (RR 2.26; 95% CI: 1.25 – 4.09) compared with ND cases, but there were no significant differences between CC and PC cases (Table 2). Of those reporting ≥1 new ReA symptom on the AReA questionnaire, 45 (75.0%) CC, 13 (68.4%) PC, and 14 (82.4%) ND cases completed the rheumatologist telephone interview (Figure 1). Non-participation at each stage of surveys was due to inability to contact participants after three attempts. Nineteen CC cases met the probable ReA case definition. Assuming no other cases occurred in the eligible population (N=224), then a minimum of 8.5% of CC cases experienced ReA. Similarly, 4 (2.8%) of 144 PC and 2 (0.6%) of 329 ND cases met the probable ReA case definition. Assuming persons

reporting new ReA symptoms on the screening questionnaire who did not complete the rheumatologist interview experienced ReA at the same rate as those interviewed, an estimated maximum of 23.9% of CC cases, 12.4% of PC cases, and 2.15% of ND cases who completed the screening questionnaire developed probable ReA (Table 2). Calculation can be referenced in Supplementary Appendix 3). The maximum ReA rates were higher among CC (RR 11.4; 95% CI: 3.13 – 41.2) and PC cases (RR 4.87; 95% CI: 1.09 – 21.8) than ND cases. There was no significant difference in maximum ReA rates between CC and PC cases.

No probable ReA cases were identified in children (aged ≤18 years) among PC and ND cases. Of CC cases, adults were not at higher risk for probable ReA compared with children (RR 1.18; 95% CI: 0.464–3.02). There was no sex predominance for probable ReA cases compared with those who did not develop ReA, even when comparing within outbreak case types. Probable ReA cases reported gastroenteritis duration lasted twice as long compared with those who did not develop ReA (median 14 vs 7 days; p<0.001). There were insufficient responses to calculate the median interval between onset of gastroenteritis and development of ReA.

Based on the rheumatologist interview, joint symptoms were the most common initial symptom in probable ReA cases. All PC and ND ReA cases and 95% of CC ReA cases developed either joint pain or swelling during the course of their disease (Table 3). Ankle (48%), knee (40%), and feet (28%) were the most common joints involved across outbreak case types. Other than eye symptoms (32%), extra-articular symptoms were uncommon. Three CC cases requiring hospitalization for severe gastroenteritis developed probable ReA. In addition, two probable ReA cases reported receiving a specialist physician diagnosis of ReA to the study rheumatologist.

DISCUSSION

We report probable ReA occurring in 8.5–23.9% of CC and 2.15–12.4% of PC cases in a large waterborne *Campylobacter* gastroenteritis outbreak in Havelock North, New Zealand caused by ovine faecal contamination of the untreated reticulated ground water system following a heavy rainfall event.[16] ReA incidence estimates following *Campylobacter* infections vary widely. One meta-analysis reported incidences from 0-24% with a summary estimate of 2.9%.[6] Larger surveillance platforms generally estimate lower ReA incidence, likely due less reporting of gastroenteritis cases to primary care than occurs in an outbreak setting where disease reporting is often enhanced.[6] Additionally, prolonged latency between gastroenteritis onset and investigation for ReA often resulted in lower ReA incidence estimates. Achieving accurate ReA estimates is challenging in population-based studies using healthcare databases because there is insufficient standardization of ICD-10 coding for ReA and inconsistent recording of related codes.[8] Outbreak-based studies have the benefit of following a similarly exposed cohort to determine ReA incidence. However, many studies prospectively follow notified gastroenteritis cases of which few are culture-confirmed,[3, 11-13] weakening associations between ReA incidences and the suspected pathogen. Furthermore, some uncultured infections in these studies could be caused by pathogens not known to precipitate ReA, further diluting the ReA incidence estimates.[8, 12, 13] Other outbreak-based studies only investigate culture-confirmed cases.[13-15] In doing this, they limit the description of ReA to affected individuals who sought medical care.

Our study design has the advantage of addressing a number of these issues by comparing three case types typically encountered in an outbreak: culture-confirmed gastroenteritis, self-reported gastroenteritis, and those exposed who do not develop diarrhoea. We found probable ReA was

more common among CC and PC cases compared with ND cases with no difference in rates between CC and PC cases. Though small PC sample size may have precluded detection of differences between CC and PC cases. Garg *et al*. investigated similar diarrhoeal presentations, including asymptomatic, self-reported gastroenteritis, and gastroenteritis presenting to medical care and found higher incidences than we report; however, their outcome of interest was new arthritis, not specifically defined as ReA.[7] They only report significant differences between medical care-seeking cases and asymptomatic cases. The trend towards higher probable ReA rates among CC cases may be associated with longer gastroenteritis duration, which may have increased the likelihood of seeking medical care and having the illness confirmed by faecal culture.

A unique feature of our study is the inclusion of rheumatologist telephone interview to confirm joint and extra-articular symptoms, leading to more refined ReA incidence estimates. Rheumatologist review is more commonly seen in population-based studies,[1, 4, 17, 18] which may be due to more available resources and less time constraints compared with outbreak-based studies. However, we demonstrate with a retention rate of 68–82% for rheumatologist telephone interview that this is a feasible method for the outbreak setting. This retention rate is substantially higher than other outbreak studies using rheumatologist examination as the sole means to estimate ReA incidence,[3, 11] and timelier than others with high rheumatologist review rates,[15] likely improving the precision of our incidence estimates. Additionally, our approach is a less resource- and labour-intensive method than those requiring rheumatologist physical examination, making it a distinct and viable option for investigating ReA in future outbreaks.

ND cases may represent asymptomatic *Campylobacter* infections as opposed to uninfected residents,[7, 12, 19] but case status remains unclear since no faecal specimens were tested in this population and some ND cases reported mild, non-diarrhoeal gastrointestinal symptoms. Multiple studies have shown that culture-confirmed infections can present without diarrhoea[20, 21] or can be asymptomatic in up to 15% of cases.[22-25] In fact, findings from one outbreak demonstrated that asymptomatic individuals exposed to a contaminated water supply developed more joint symptoms than an unexposed population.[19] Others have reported 8–10% of asymptomatic individuals who consumed contaminated food during Salmonella outbreaks developed ReA.[9, 26] Although ND cases may represent outbreak-related infections, our results are consistent with previous findings that individuals without diarrhoea are at lower risk for developing ReA compared with those who experience diarrhoea.[19, 26]

Although PC and ND cases were more likely to be older and female, we found no sex or age differences in the probable ReA cases compared with those who did not develop ReA. This is in contrast with recent studies reporting a predominance of females[1, 4, 11, 18] and higher ReA incidence among adults compared with children;[1, 12] Most probable ReA cases presented with mild symptoms and few sought medical care, consistent with previous *Campylobacter* outbreaks.[4, 11, 13] As with previous studies, knee and ankle were the sites most commonly involved[1-3, 13] and extra-articular manifestations were rare.[11] Data on the association between gastroenteritis severity and development of ReA are conflicting. Probable ReA cases had longer duration than those without ReA. Similarly, many have shown higher severity[1, 2] and longer duration of gastroenteritis[4, 9, 12, 26] associated with higher risk of ReA development, whereas others have shown no association.[2, 4, 13, 14]

This study had several limitations. Post-outbreak whole genome sequencing revealed that outbreak-related campylobacteriosis cases likely had onset dates between August 7 – 24 [16]. Given limitations in our enrolment design, we were unable to amend our outbreak period. This would have little impact on ReA rates attributed to CC cases because each is culture-confirmed campylobacteriosis; however, inclusion of PC cases beyond the true outbreak period may have over attributed diarrheal cases to campylobacteriosis in 22 PC cases, including 2 cases with probable ReA. Our screening phone survey response rates were not as high as some studies using similar methods,[9, 12] and use of a landline sampling frame may have reduced recruitment of younger and economically-deprived households. These biases as well as willingness to participate could impact the comparison of minimum ReA rates between groups, so we chose to compare maximum ReA rates because this analysis would be primarily limited by participation bias.

Cases were not examined by a rheumatologist and classification of joint involvement was dependent on a patient's self-report, preventing definitive diagnosis of ReA. It is possible that individuals seeking medical care, such as CC cases, were more likely to report medical conditions and symptoms, including ReA symptoms. In the absence of physical examination by a rheumatologist, this bias could contribute to the trend towards higher ReA incidence seen in this population.[7] Furthermore, these individuals may be more likely to report more gastroenteritis symptoms during the survey, potentially biasing the association between gastroenteritis severity and ReA development.[18]

Given resource limitations, we were unable to perform follow-up assessments of existing cases to assess disease remission and chronicity. Although the timeliness of our survey likely reduced recall bias compared with other studies,[9, 15] it also prohibited identification of incident cases

occurring greater than 12 weeks following the outbreak. Ternhag *et al.* demonstrated that initial ReA surveillance identified few cases at 3 months, but follow-up 1 year revealed new, associated cases.[27] Also, although we compared CC and PC cases with ND cases, we did not have the resources to study an unexposed, control group. As such, we have no ReA baseline incidence with which to compare our rates.[19] We did not have resources to screen HLA-B27 prevalence, which has known association with ReA development and may have affected the rates seen in our cohort.[28]

Our findings have several important implications. They underscore the importance of advising populations affected by *Campylobacter* outbreaks that delayed effects can occur. These individuals and doctors should be alerted to the risk of ReA following *Campylobacter* outbreaks. As ReA impacts short- and long-term health outcomes, outbreak-associated economic assessments should consider including costing for this sequela.[29]

In summary, we present a high probable ReA incidence among a spectrum of gastroenteritis case types during a very large *Campylobacter* gastroenteritis outbreak, providing a comprehensive characterisation of ReA in an exposed population. We describe a screening survey and rheumatologist review method that provides a more refined approach than use of a screening questionnaire alone. This method serves as a practical and resource-efficient alternative to in-person rheumatologic exams and is a feasible option for estimation of ReA burden in future gastroenteritis outbreaks.

Figure 1. Reactive arthritis (ReA) surveillance following Havelock North *Campylobacter* gastroenteritis outbreak: Screening questionnaire and rheumatologist interview enrolment

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Data Sharing Statement. No additional data are available.

Contributorship and Guarantorship Statement

Tiffany Walker- Led surveillance, assisted with study design, conducted analysis, performed literature review, drafted manuscript. Dr. Walker serves as the guarantor.

Rebecca Grainger- Assisted with literature review, assisted with study design, conducted rheumatologic interviews, assisted with interpretation of findings, reviewed manuscript.

Terry Quirke- Assisted with study design, assisted with data analysis, assisted with interpretation of findings, reviewed manuscript.

Rebekah Roos- Assisted with literature review, assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Jill Sherwood- Assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Graham Mackereth- Conducted household survey, assisted with study design, assisted with data analysis, assisted with interpretation of findings, reviewed manuscript.

Tomasz Kiedrzynski- Assisted with household study design, assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Rachel Eyre- Assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Shevaun Paine- Assisted with household study design, assisted with study design, assisted with interpretation of findings, reviewed manuscript.

Tim Wood- Assisted with household study design, assisted with interpretation of findings, reviewed manuscript.

Anita Jagroop- Assisted with interpretation of findings, reviewed manuscript.

Michael G. Baker- Assisted with interpretation of findings, reviewed manuscript.

Nicholas Jones- Provided project oversight, assisted with interpretation of findings, reviewed manuscript.

References

1. Townes JM, Deodhar DA, Swanson E, Smith K, Krug HE, Barkhuizen A, et al. Reactive arthritis following culture-confirmed infections with bacterial enteric pathogens in Minnesota and Oregon: A population-based study. *Annals of Rheumatic Diseases* 2008;67(12):1689–96.
2. Schönberg-Norio D, Mattila L, Lauhio A, et al. Patient-reported complications associated with Campylobacter jejuni infection. *Epidemiol Infect* 2010;138(7):1004–11.
3. Hannu T, Kauppi M, Tuomala M, et al. Reactive arthritis following an outbreak of Campylobacter jejuni infection. *J Rheumatol* 2004;31(3):528–30.
4. Hannu T, Mattila L, Rautelin H, et al. Campylobacter-triggered reactive arthritis: a population-based study. *Rheumatology* 2002;41(3):312–18.
5. Ajene AN, Fischer Walker CL, Black RE. Enteric pathogens and reactive arthritis: a systematic review of Campylobacter, salmonella and Shigella-associated reactive arthritis. *J Health Popul Nutr* 2013;31(3):299–307.
6. Keithlin J, Sargeant J, Thomas MK, et al. Systematic review and meta-analysis of the proportion of Campylobacter cases that develop chronic sequelae. *BMC Public Health* 2014;14:1203.
7. Garg AX, Pope JE, Thiessen-Philbrook H, et al. Arthritis risk after acute bacterial gastroenteritis. *Rheumatology* 2008;47(2):200–04.
8. Curry JA, Riddle MS, Gormley RP, et al. The epidemiology of infectious gastroenteritis related reactive arthritis in U.S. military personnel: a case-control study. *BMC Infectious Diseases*.2010;10:266.
9. Locht H, Krogfelt K. Comparison of rheumatological and gastrointestinal symptoms after infection with Campylobacter jejuni/coli and enterotoxigenic Escherichia coli. *Annals of the Rheumatic Diseases* 2002;61(5):448–52.

10. Buxton JA, Fyfe M, Berger S, et al. Multiprovincial Salmonella typhimurium Case-Control Study Group. Reactive arthritis and other sequelae following sporadic Salmonella typhimurium infection in British Columbia, Canada: a case control study. *J Rheumatol* 2002;29(10):2154–58.
11. Uotila T, Antonen J, Laine J, et al. Reactive arthritis in a population exposed to an extensive waterborne gastroenteritis outbreak after sewage contamination in Pirkanmaa, Finland. *Scand J Rheumatol* 2011;40(5):358–62.
12. Arnedo-Pena A, Beltrán-Fabregat J, Vila-Pastor B, et al. Reactive arthritis and other musculoskeletal sequelae following an outbreak of Salmonella hadar in Castellon, Spain. *J Rheumatol* 2010;37(8):1735–42.
13. Locht H, Mølbak K, Krogfelt KA. High frequency of reactive joint symptoms after an outbreak of Salmonella enteritidis. *J Rheumatol* 2002;29(4):767–71.
14. Rohekar S, Tsui FW, Tsui HW, et al. Symptomatic acute reactive arthritis after an outbreak of salmonella. *J Rheumatol* 2008;35(8):1599–602.
15. Lee AT, Hall RG, Pile KD. Reactive joint symptoms following an outbreak of Salmonella typhimurium phage type 135a. *J Rheumatol* 2005;32(3):524–27.
16. Gilpin BJ, Walker T, Paine S, et al. A large scale waterborne Campylobacteriosis outbreak, Havelock North, New Zealand [published online ahead of print, 2020 Jun 29]. *J Infect*. 2020;S0163-4453(20)30445-X.
17. Hannu T, Mattila L, Siitonen A, et al. Reactive arthritis attributable to Shigella infection: a clinical and epidemiological nationwide study. *Annals of the Rheumatic Diseases* 2005;64(4):594–98.
18. Schiellerup P, Krogfelt KA, Locht H. A comparison of self-reported joint symptoms following infection with different enteric pathogens: effect of HLA-B27. *J Rheumatol* 2008;35(3):480–87.

19. Laine J, Uotila T, Antonen J, et al. Joint symptoms after a large waterborne gastroenteritis outbreak—a controlled, population-based questionnaire study. *Rheumatology 2012*;51(3):513–18.

20. Amour C, Gratz J, Mduma E, et al. Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) Network Investigators. Epidemiology and Impact of Campylobacter Infection in Children in 8 Low-Resource Settings: Results From the MAL-ED Study. *Clin Infect Dis* 2016;63(9):1171–79.

21. Mason J, Iturriza-Gomara M, O'Brien SJ, et al. Campylobacter Infection in Children in Malawi Is Common and Is Frequently Associated with Enteric Virus Co-Infections. *PLoS ONE* 2013;8(3):e59663.

22. Komba EV, Mdegela RH, Msoffe PL, et al. Prevalence, Antimicrobial Resistance and Risk Factors for Thermophilic Campylobacter Infections in Symptomatic and Asymptomatic Humans in Tanzania. *Zoonoses Public Health* 2015;62(7):557–68.

23. Lääveri T, Antikainen J, Pakkanen SH, et al. Prospective study of pathogens in asymptomatic travellers and those with diarrhoea: aetiological agents revisited. *Clin Microbiol Infect* 2016;22(6):535–41.

24. Lindblom GB, Ahrén C, Changalucha J, et al. Campylobacter jejuni/coli and enterotoxigenic Escherichia coli (ETEC) in faeces from children and adults in Tanzania. *Scand J Infect Dis* 1995;27(6):589–93.

25. Zaidi MB, McDermott PF, Campos FD, et al. Antimicrobial-resistant Campylobacter in the food chain in Mexico. *Foodborne Pathog Dis* 2012;9(9):841–47.

26. Dworkin MS, Shoemaker PC, Goldoft MJ, et al. Reactive arthritis and Reiter's syndrome following an outbreak of gastroenteritis caused by Salmonella enteritidis. *Clin Infect Dis* 2001;33(7):1010–14.

27. Ternhag A, Törner A, Svensson Å, et al. Short- and Long-term Effects of Bacterial Gastrointestinal Infections. *Emerging Infectious Diseases* 2008;14(1):143–48.

28. Hannu T, Mattila L, Rautelin H, Pelkonen P, Lahdenne P, Siitonen A, et. al. Campylobacter-triggered reactive arthritis: a population-based study. *Rheumatology* 2002;41(3):312-8

29. Moore D, Drew R, Davies P, et al. The Economic Costs of the Havelock North August 2016 Waterborne Disease Outbreak, Report prepared for the Ministry of Health. Sapere Research Group Ltd., Wellington, NZ. September 2020. https://www.health.govt.nz/publication/economic-costs-havelock-north-august-2016-waterborne-disease-outbreak. Accessed 5/2020.

Table 1. Demographic and clinical characteristics of reactive arthritis (ReA) surveillance enrolees and probable ReA cases by outbreak case type

	All ReA surveillance enrolees				Probable ReA cases		
Participant characteristics	**CC* (N=106)**	**PC* (N=47)**	**ND* (N=113)**	**p-value**	**CC* (N=19)**	**PC* (N=4)**	**ND* (N=2)**
Female	48 (45%)	31 (66%)	74 (65%)	<0.001	8 (42%)	2 (50%)	2 (100%)
Age, median (range)	47 (1–96)	55 (15–85)	62 (16–99)	<0.001	43 (10–73)	69 (54–78)	68 (49–86)
≤18 years	28 (26%)	1 (2%)	1 (1%)		5 (26%)	0	0
>18 years	78 (74%)	46 (98%)	112 (99%)		14 (74%)	4 (100%)	2 (100%)
Race/Ethnicity				<0.001			
Maori	7 (7%)	2 (4%)	0		1 (5%)	0	0
Pacific Islander	2 (%)	0	0		1 (5%)	0	0
NZ European	85 (80%)	38 (81%)	97 (86%)		17 (89%)	4 (100%)	1 (50%)
Other European	8 (8%)	6 (13%)	16 (14%)		0	0	1 (50%)
Asian	3 (3%)	1 (2%)	0		0	0	0
Other	1(1%)	0	0		0	0	0
Gastroenteritis symptoms[¥]				<0.001			
0	13 (12%)	8 (17%)	101 (89%)		1 (5%)	2 (50%)	0
1	14 (13%)	10 (21%)	6 (5%)		0	1 (25%)	0
2	17 (16%)	15 (32%)	3 (3%)		2 (11%)	1 (25%)	2 (100%)
3	39 (37%)	9 (19%)	3 (3%)		7 (37%)	0	0
4	23 (22%)	5 (11%)	0		9 (47%)	0	0
Gastroenteritis duration, median (range) [γ]	10 (2–62)	7 (1–31)	3 (1–17)	0.0014	14 (3–62)	10 (4–28)	2 (2)

*CC: confirmed campylobacteriosis case; PC: probable campylobacteriosis case; ND: No diarrhoea case

[¥]Includes fever, nausea, vomiting, abdominal pain

[γ]missing gastroenteritis duration for 5 confirmed campylobacter and 1 probable campylobacter case from all ReA enrolees; missing gastroenteritis duration for 1 probable and 1 no diarrhoea probable ReA case

Table 2. New ReA symptom and probable reactive arthritis (pReA) incidence among outbreak case types following Havelock North *Campylobacter* gastroenteritis outbreak

Case Type	≥1 New ReA symptom	RR (95% CI)*¥	RR (95% CI)ɣ	Maximum pReA Rate	RR (95% CI)*¥	RR (95% CI)ɣ
CC	56.6%	3.76 (2.35–6.01)	1.40 (0.95–2.06)	23.9%	11.4 (3.13– 41.2)	2.22 (0.90–5.43)
PC	40.4%	2.26 (1.25–4.09)		12.4%	4.87 (1.09 – 21.8)	
ND	15.0%			2.15%		

*RR: relative risk; CI: confidence interval; CC: confirmed campylobacteriosis case; PC: probable campylobacteriosis case; ND: No diarrhoea case

¥compared with no diarrhoea cases

ɣcompared with probable campylobacteriosis cases

Table 3. Clinical characteristics among probable reactive arthritis (ReA) cases by outbreak case type

Rheumatologic symptoms	CC* (N=19)	PC* (N=4)	ND* (N=2)	All probable ReA (N=25)
Initial symptom				
Joint	15 (79%)	4 (100%)	2 (100%)	21 (84%)
Eye	1 (7%)	0	0	1 (4%)
Oral	1 (7%)	0	0	1 (4%)
Joint symptoms				
Pain	18 (95%)	4 (100%)	2 (100%)	24 (96%)
Swelling	8 (42%)	2 (50%)	2 (100%)	11 (44%)
Pain or Swelling	18 (95%)	4 (100%)	2 (100%)	24 (96%)
Number of swollen joints¥				
0	11 (58%)	2 (50%)	0	7 (28%)
1	2 (11%)	1 (25%)	1 (50%)	4 (16%)
2	3 (16%)	0	0	5 (20%)
3	0	1 (25%)	0	4 (16%)
4	1 (5%)	0	0	1 (4%)
5	0	0	0	0
6	0	0	1 (50%)	1 (4%)
Joint sites**				
Hand	4 (21%)	1 (25%)	0	5 (20%)
Wrist	3 (16%)	1 (25%)	0	4 (25%)
Elbow	4 (21%)	1 (25%)	0	5 (20%)
Shoulder	2 (11%)	1 (25%)	0	3 (12%)
Feet	5 (26%)	1 (25%)	1 (50%)	7 (28%)
Ankle	10 (53%)	0	2 (100%)	12 (48%)
Knee	6 (32%)	3 (75%)	1 (50%)	10 (40%)
Hip	5 (26%)	0	1 (50%)	6 (24%)
Back	4 (21%)	1 (25%)	1 (50%)	6 (24%)
Extra-articular symptoms				
Heel	2 (11%)	1 (25%)	0	3 (12%)

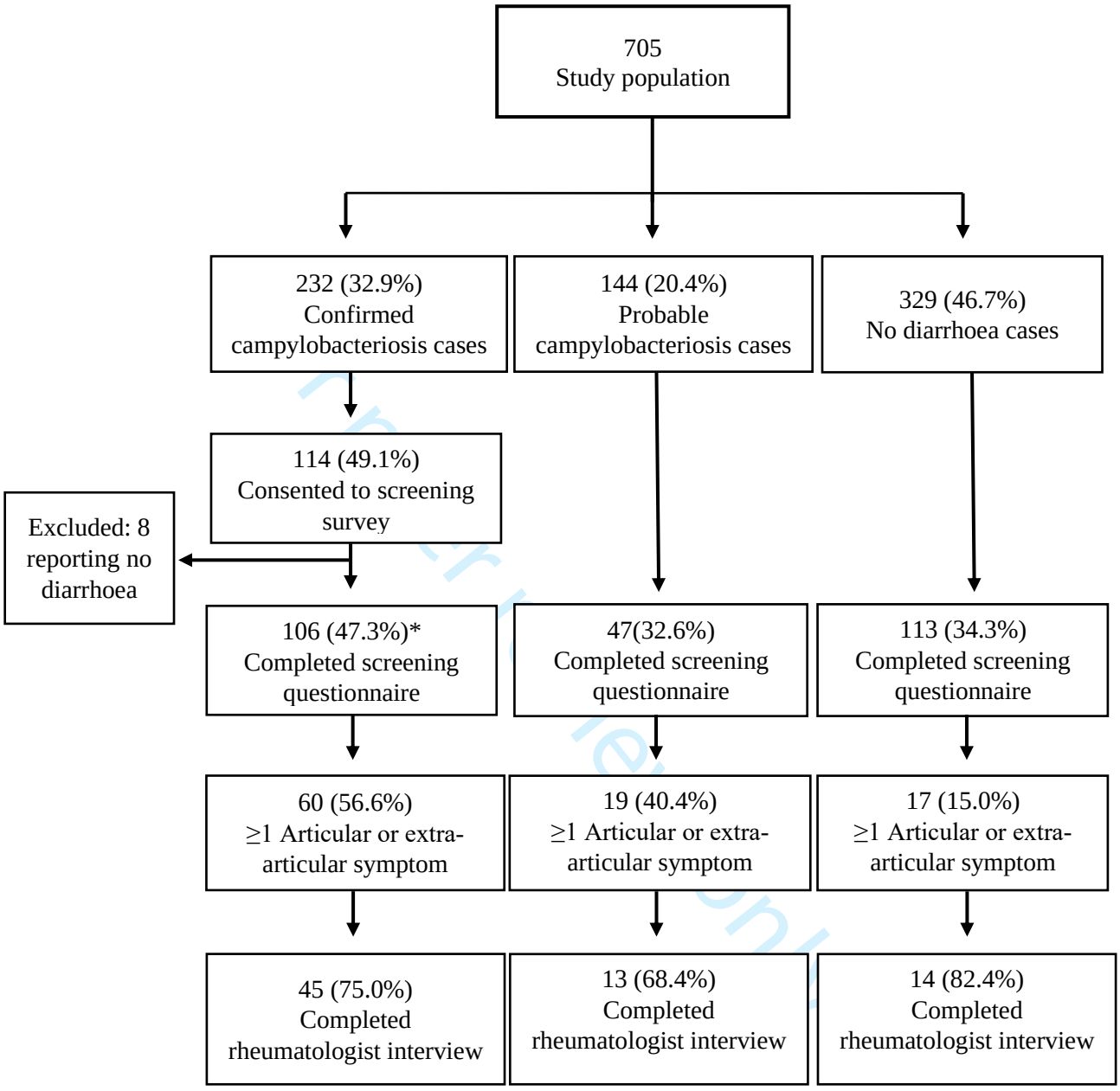
Other tendon	1 (5%)	0	1 (50%)	2 (8%)
Mouth ulcers	4 (21%)	0	0	4 (16%)
Sore eyes	6 (32%)	0	2 (100%)	8 (32%)
Conjunctivitis	3 (16%)	0	1 (50%)	4 (16%)
Morning stiffness	13 (68%)	4 (100%)	1 (50%)	18 (72%)
<1 hour	9	3	1	13 (52%)
≥ 1 hour	4	1	0	5 (20%)

*CC: confirmed campylobacteriosis case; PC: probable campylobacteriosis case; ND: No diarrhoea case

¥ missing number of joints affected in two CC cases reporting joint swelling

**Includes joint pain or swelling

Figure 1. Reactive arthritis (ReA) surveillance following Havelock North *Campylobacter* gastroenteritis outbreak: Screening questionnaire and rheumatologist interview enrolment



*Percent calculated from confirmed campylobacteriosis cases reporting diarrhoea (N=224)

Supplementary Appendix 1. Adapted AReA Telephone Screening Questionnaire

1. Were you exposed to the Havelock North reticulated water supply [including drinking water or using water to prepare food] from 5th to 12th August 2016?

□ Yes □ No [If No, no further information is required].

2. Did you experience any of the following symptoms between 5th August and 6th September?

□ Diarrhoea □ Vomiting □ Abdominal Pain □ Fever (38C) □ Nausea □ None

3. If you had symptoms, what was the first date you had diarrhoea, vomiting, abdominal pain, nausea or fever related to your infection? _____

4. If you had symptoms, what was the duration of your illness? _____ (days)

6. If you had symptoms, were you prescribed antibiotics for the illness? □ Yes □ No

If yes, what antibiotics?_____

For the rest of the survey, I would like to ask you about symptoms that you may have had since the outbreak started that may indicate whether you had a condition called Reactive Arthritis. This is a disease that can occur after a diarrhoeal illness and is not limited to joint pains. If you had diarrhoea, I am asking about symptoms that occurred AFTER you were sick with diarrhoea.

Since the start of the outbreak, have you experienced ANY of the following symptoms for 3 consecutive DAYS or more?

7. Joint pain, swelling or stiffness?	Yes	No
8. Visibly swollen joints?	Yes	No
9. Swollen joints which could not be straightened out?	Yes	No
10. Stiffness in the joints for half hour or m	Yes	No
11. Heel pain?	Yes	No
12. Red, itchy, or burning eyes?	Yes	No
13. Painful mouth ulcers?	Yes	No
14. Rash on genitals?	Yes	No
15. Discharge from genitals or burning on urination?	Yes	No

16. Rash on palms or soles/	Yes	No

17. What was the first date these symptoms started? (If you had diarrhoea, this would be the first date you noticed these symptoms AFTER your diarrhoea started)_____(dd/mm/yy)

18. Information from this survey will be reviewed by a medical specialist to determine whether your symptoms are concerning for reactive arthritis. If so, you are eligible to be recontacted by telephone to be interviewed by the medical specialist. She will ask you additional questions about your symptoms to confirm or rule out the diagnosis of reactive arthritis. Would you be willing to participate in the follow-up interview if you meet the criteria? □ Yes □ No

Supplementary 2. Rheumatologist Telephone Interview Questionnaire

Details of suspected Reactive arthritis and related extra-articular features

1. What was the first symptom? (please circle): joint / oral / eye / genital / skin
2. What was the date of their first new symptom? _____

Musculoskeletal features:

3. Has the patient experienced joint pain? □ Yes □ No
4. Have any joints been swollen? □ Yes □ No
5. How many joints were swollen? _____
6. Which areas were painful or swollen (please tick):

SITE	INVOLVED (Y/N)	PAIN (Y/N)	SWELLING (Y/N/NA)	SIDE (R/L/B/NA)	SEQUENCE (1^{ST}, 2^{ND}, ALL, NA)	DURATION (DAYS)	RESOLVED (Y/N)
Hands							
Wrists							
Elbow							
Shoulder							
Feet							
Heel							
Ankle							
Knee							
Hip							
Back							
Tendons							

7. Has the person experienced MORNING joint stiffness? □ Yes □ No

   7 b. If yes, please indicate duration of MORNING joint stiffness_____ (minutes/hours/all day)

8. Has the person had painful tendon insertion sites? □ Yes □ No
   8b. If yes please state sites/s_____

Oral features:

9. Has the person had any mouth ulcers? □ Yes □ No

Eye features:

10. Has the person had:
    a. Sore eyes? □ Yes □ No
    b. Conjunctivitis? □ Yes □ No
    c. Uveitis? □ Yes □ No

Genital features:

11. Has the person had:
    a. Urinary symptoms? □ Yes □ No
    b. Urethritis □ Yes □ No
    c. Circinate balanitis? □ Yes □ No

Skin features:

12. Has the person had:
    a. New skin rash of palms of hands? □ Yes □ No
    b. New skin rash of soles of feet? □ Yes □ No
13. Keratoderma blennorrhagia? □ Yes □ No
14. Other_____

Supplementary Appendix 3. Calculation of Maximum Probable ReA Rate

[[(Rate of probable ReA)*(Participants with ≥1 ReA symptom who did not participate in Rheumatologist interview)] + Probable ReA cases]/Enrollees in AReA screening survey

CC: [[(19/45)*(60-45)] +19]/106

PC: [[(4/13)*(19-13)] +4]/47

ND: [[(2/14)*(17-14)] +2]/113

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/a
		(*e*) Describe any sensitivity analyses	N/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8, Table 1, 3
Outcome data	15*	Report numbers of outcome events or summary measures	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.