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Risk factors for ciprofloxacin resistance in reported *Campylobacter* infections in southern Alberta

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SUMMARY

We conducted a case-control study examining risk factors for ciprofloxacin resistance in *Campylobacter* infections that were reported in 2004 and 2005 in two health regions in southern Alberta. The study questionnaire included questions about recent travel and antibiotic use, food consumption frequency, use of household and personal hygiene products with antibacterial agents, contact with animals, and potential misuse of antibiotics. Of the 210 patients who participated, 31·0% had ciprofloxacin-resistant *Campylobacter* infections. Foreign travel was the strongest predictor of resistance. Surprisingly, possession of antibiotics for future use was identified as a risk factor for resistance. We also examined the potential for participation bias and resistance misclassification to affect the resulting multivariable models. Participation bias appears to have had a substantial effect on the model results, but the estimated misclassification effect due to the use of different ciprofloxacin susceptibility testing methods was only slight.

INTRODUCTION

Fluoroquinolone antibiotics, such as ciprofloxacin, have been recommended by some authorities for the empirical treatment of infectious diarrhoea [1]. Such recommendations often carry cautions against overuse, and use when not indicated to minimize risk of the development of resistance in enteric bacteria such as *Campylobacter*. There are many reports of increasing resistance to fluoroquinolones in *Campylobacter* strains from humans and foods and food animals [2–5]. Of specific concern are reports of high levels of resistance in strains in developing parts of the world, and in strains isolated from travellers who have returned from developing countries [6–8]. Case-control studies have investigated risk factors for fluoroquinolone resistance in *Campylobacter* infections in Europe and the United States. Results vary, but the primary risk factor reported is foreign travel [7, 9, 10].

Within southern Alberta are the Chinook Health Region (population 152 000) and the Calgary Health Region (population 1 122 000) [11, 12]. The Chinook region has a large agricultural base and many workers in the livestock industry, while the Calgary region has one of the most rapidly growing metropolitan populations in Canada [13]. The incidence of *Campylobacter* infection in humans is relatively high in these health regions. In 2000, in both regions there were about 70 infections/100 000; higher than

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the province-wide incidence of 42·5/100 000 [14]. Thus, these health regions present a good location in which to investigate the relative importance of a number of risk factors for ciprofloxacin resistance in *Campylobacter* infections.

MATERIALS AND METHODS

Study participants

Study participants were residents of the Chinook Health Region and Calgary Health Region, aged >16 years, who submitted a stool sample that was positive for the presence of *Campylobacter*, and who were followed-up by a public health nurse or inspector between 1 February 2004 and 29 July 2005. Verbal consent was recorded prior to administration of the study questionnaire. Ethics approval was granted for this study by the Health Research Ethics Board, Panel B, University of Alberta, Edmonton, Alberta, the Conjoint Health Research Ethics Board, University of Calgary, Calgary, and the Chinook Health Region Regional Research Committee, Lethbridge.

Questionnaire description and administration

All questions for the study questionnaire were open-ended and required one-word answers. Potential risk factors included travel within the previous month to destinations outside Canada and the United States, average 2-week consumption of specific foods, frequency of eating in restaurants, drinking unpasteurized milk or untreated water, exposure to animal manure or faeces, administration of an antibiotic to animals or humans, and antibiotics used within the past month. We also included questions about exposure to household products and personal hygiene items containing antibacterial agents, which could increase risk of antibiotic resistance [15]. In addition, we investigated the hypothesized resistance risks associated with possession of antibiotics that the patient had saved for future use (referred to here as possession of non-prescribed antibiotics), which we used as an indicator for the potential for inappropriate self-medication, and living more than 8 km from a pharmacy (rural residence), which could increase the potential for self-medication. Other data gathered included age, sex, education, occupation, details about any antibiotic treatment, and knowledge of antibiotic susceptibility testing results. Public health nurses in the Chinook Health Region and public health inspectors in the Calgary Health Region were instructed on correct administration of the scripted questionnaire. Questionnaires were administered by phone during routine follow-up investigations by the public health officials.

Quinolone susceptibility testing

Susceptibility testing at the Chinook Health Region Laboratory used a modified Kirby–Bauer method, in which colonies were streaked onto Mueller–Hinton agar (BD Diagnostics, Oakville, ON, Canada) with 5% sheep blood (BD Diagnostics) and incubated at 37–42 °C for 24–48 h, depending on growth characteristics. The zone of inhibition around a 5 μg ciprofloxacin disk (BD Diagnostics) was assessed as follows: $\leqslant$15 mm, resistant; 16–20 mm, intermediate; $\geqslant$21 mm, susceptible. *Campylobacter* strains isolated in the Calgary Health Region by Calgary Laboratory Services were tested for nalidixic acid susceptibility using 30 μg nalidixic acid disks (Oxoid, Nepean, ON, Canada) on blood agar plates (PML Microbiologicals, Wilsonville, OR, USA). Susceptibility to nalidixic acid was assessed by zone diameter $\geqslant$20 mm. Plates were incubated at 42 °C for 18–24 h.

Data handling

Data were double-entered into SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Cases were participants from whom ciprofloxacin- or nalidixic acid-resistant *Campylobacter* were isolated, and controls were those from whom ciprofloxacin- or nalidixic acid-susceptible strains were isolated. Illnesses that started at least 2 days after the first day of travel outside the United States and Canada and within 3 days of returning from travel were considered to be caused by foreign strains. This criterion is based on the assumption of a typical 2- to 3-day incubation period for infection [16, 17]. When multiple travel destinations were given, the most probable country where an infection was acquired was determined from the individual's travel timeline and illness onset information.

Criteria for empirical treatment with an antibiotic or fluoroquinolone included either a positive response to the question 'Did you start taking the antibiotic before submitting a stool sample?' or a course of treatment for the diarrhoeal illness starting $\geqslant$1 days before the date of stool sample submission (extracted from laboratory data). In addition, the patient must

have provided the name of their medication, which had to be a recognized antibiotic.

Food consumption frequency data were gathered on a continuous scale, but for modelling purposes, data for most food types were classified as low, medium, or high consumption frequency based on tertiles (three equal divisions of the study population) of the data. Cut-off points for food consumption categorical variables among domestic infections were changed because the distribution of reported frequency of consumption for this group differed from that of the total study sample. Abbreviations for selected variables are given in Table 1.

Logistic regression modelling

Univariate logistic regression models were fitted for each independent variable using the SPSS LOGISTIC REGRESSION function. Along with the crude odds ratios (OR) and 95% confidence intervals (CI) for potential risk factors, ORs adjusted for age, sex, health region, higher education, season, and rural residence were calculated. Three sets of univariate analyses were conducted using the following datasets: (A) all participants, (B) participants with domestically acquired infections, and (C) participants infected from 1 February 2004 to 31 January 2005 (referred to as 2004 infections). Analysis with dataset C controlled any effect of unequal sampling over 2004 and 2005.

A multivariable model was developed using dataset A. Candidate variables were those with a crude (unadjusted) univariate Wald value significant at the 10% level. Final model variables were selected using backwards and forwards stepwise logistic regression model-building approaches, with a P entry value of 0·20, and P removal value of 0·25. Interaction terms were selected from all biologically reasonable pairs of multiplicative effect variables through likelihood ratio testing for a difference at the 10% level and stepwise logistic regression modelling using the previously mentioned entry and removal values. Confounders were identified and added to the base model if, when added to the model, an exposure variable β-coefficient changed by $>10\%$. When the standardized residual for any data-point was outside the 0·1% level of significance, it was removed as an outlier.

Violations of the assumption of sampling adequacy, which is integral to logistic regression modelling, was assessed when $>20\%$ of cell values in a contingency table were <5. Multivariable models using datasets B and C were not attempted because $>50\%$ of the candidate variables for the base models violated the sampling adequacy assumption. All final results of univariate and model analyses were assessed for significance at the 5% level. Models were assessed with and without inverse probability weighting to adjust for unequal sampling across seasons. Weights were as follows: spring, 0·5, summer, 0·71, autumn, 1·0, winter, 0·65.

Validity assessments

To assess the effect of participation bias, nalidixic acid resistance and travel data for 161 eligible non-participating patients in the Calgary Health Region from September 2004 to July 2005 were acquired from the health region and were compared to participant data. Patient identifiers and any other data from non-participants were not released from the health region. Non-participating patients were those who were aged >16 years and who completed the health region's enteric follow-up investigation but were not asked, or declined to participate in the case-control study. To account for the potential impact of participation bias, the $OR_{foreign}$ was adjusted by dividing with a selection bias factor [equation (1)] [18], and this was compared to the unadjusted OR.

$$\frac{S_{AF}S_{BD}}{S_{AD}S_{BF}}, \quad (1)$$

where S_{AF} = proportion of participants among cases with foreign strains; S_{BD} = proportion of participants among controls with domestic strains; S_{AD} = proportion of participants among cases with domestic strains; S_{BF} = proportion of participants among controls with foreign strains.

The difference in susceptibility testing methods used in the two health regions was a concern; the less specific nalidixic acid disk method used in the Calgary Health Region could have resulted in an artificially high proportion of ciprofloxacin resistance in *Campylobacter* strains in that region. Possible resistance misclassification was addressed by applying the Greenland estimation [18], [equation (2)], to estimate the number of potentially misclassified ciprofloxacin-resistant strains in the Calgary Health Region. We randomly selected this number of participants from those with resistant strains in this health region, and generated an altered dataset in which susceptibility was imputed for those individuals. This was repeated nine more times and the final multivariable model

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Table 1. *Definition of some study independent variables and abbreviations used in text and tables*

Name	Abbreviated name	Definition	Units
Foreign travel-related infection	Foreign	Symptoms started at least 2 days after the first day of travel outside the United States and Canada and within 3 days of returning	Yes, no
Macro-region of infection source country	Macro-region	Macro-region of country in which infection occurred	n.a.
Empirical treatment with an antibiotic or fluoroquinolone	None	Participant reported taking an antibiotic or fluoroquinolone prior to submitting a stool sample, or this was indicated by laboratory and questionnaire data	Yes, no
Possession of non-prescribed antibiotics	None	Participant possesses antibiotics that were not prescribed for them that were saved for future use	Yes, no
Living more than 8 km from a pharmacy	Rural residence	Used as an indicator for the potential for antibiotic self-medication	Yes, no
Food consumption frequency	(Name of food) consumption	Typical number of meals consumed in a 2-week period; raw data for all foods except shellfish grouped into tertiles	Low, medium, high

n.a., Not applicable; independent variable has no units.
The study questionnaire is available upon request.

was run on the ten altered datasets, and the percent difference between the mean OR values from the altered data and the OR values from the original data was calculated. Values for Se and Sp were extracted from the report by Gaudreau & Gilbert [19].

$$A = \frac{A^* - \mathrm{Fp}N}{\mathrm{Se} + \mathrm{Sp} + 1}, \quad (2)$$

where A = adjusted number of fluoroquinolone-resistant strains; A^* = observed number of fluoroquinolone-resistant strains; Fp = false positive probability; N = number of affected strains; Se = probability that resistant strains were classified as resistant; Sp = probability that susceptible strains were classified as susceptible.

RESULTS

Study participants and *Campylobacter* strains

Based on public health databases from the study area, about 600 cases of *Campylobacter* infections in people aged >16 years were reported to the health regions during the study period. Manpower shortages in the Calgary Health Region precluded public health inspectors from asking all patients to participate. One *Campylobacter* outbreak occurred during the study period; outbreak patients were not asked to participate in the study. The number of patients who were asked to participate was 351. In total, 229 patients consented to participate in the study, representing about 38% of all potentially eligible people and 65% of all who were asked to participate. Lack of time was the most common reason given for refusing to participate. Nineteen patients were censored due to lack of stool sample submission data.

The mean age of participants was 40·0 years, 64·8% (n = 210) had college or university education, 16·2% reported occupational handling of animals, and 17·1% were rural residents. Among the 210 *Campylobacter* isolates from study participants, 196 (93·3%) were *C. jejuni*, six (2·9%) were *C. coli*, and the species of eight strains (3·8%) was not determined. Most strains (80·5%) were from people reporting in the Calgary Health Region, and 68 infections (32·4%) were acquired outside the United States and Canada, while the remaining 142 were probably acquired domestically. The proportion of ciprofloxacin-resistant strains among all strains was 31·0% (n = 210). Resistant strains were more common in infections caused by strains other than *C. jejuni*, in infections in participants who had higher education, who lived in the Calgary Health Region, and who were male (Table 2).

Individual risk factors

Results from adjusted univariate models are summarized in Table 3 (all participants) and Table 4

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Table 2. *Distribution of ciprofloxacin-resistant* Campylobacter *cases and ciprofloxacin-susceptible* Campylobacter *controls in southern Alberta, 1 February 2004–29 July 2005* ($n=210$)

Variable (n)	Cases (%)	Controls (%)	P value*
Sex			0·05
Female (95)	37·9	62·1	
Male (114)	25·4	74·6	
Age (yr)			0·3
<28 (48)	37·5	62·5	
28–37 (55)	21·8	78·2	
38–49 (53)	35·8	64·2	
⩾50 (54)	29·6	70·4	
College or university education			0·4
No (74)	27·0	73·0	
Yes (136)	33·1	66·9	
Season of reported infection			<0·001
Summer (76)	17·1	82·9	
Autumn (24)	20·8	79·2	
Winter (28)	60·7	39·3	
Spring (82)	36·6	63·4	
Health region			0·01
Chinook (41)	14·6	85·4	
Calgary (169)	34·9	65·1	
Rural residence†			0·2
No (171)	32·8	67·2	
Yes (36)	22·2	77·8	
C. jejuni infection			0·03
No (14)	57·1	42·9	
Yes (196)	29·1	70·9	

* Significance of the χ^2 Pearson statistic.
† Refer to Table 1 for variable description.

(2004 infections). Two risk factors were associated with ciprofloxacin resistance: recent travel outside Canada and the United States and possession of non-prescribed antibiotics. Furthermore, possession of non-prescribed antibiotics was the only univariate risk factor identified among infections probably acquired domestically (adjusted OR 18·5, 95% CI (OR) 1·8–186·3, $P=0·01$; $n=142$). Risk levels were highly variable among travel destination macro-regions (Table 3). Empirical treatment with an antibiotic or a fluoroquinolone, use of antibacterial dishwashing soap or antibacterial toothpaste, contact with animals, and handling of antibiotics were not risk factors for ciprofloxacin resistance at the 5% level. None of the variables for frequency of food consumption were significant risk factors.

Multivariable logistic regression analysis

Candidate variables for stepwise model-building included: gender, season, health region, *C. jejuni*, foreign, empirical treatment with a fluoroquinolone, cattle handling, and possession of a non-prescribed antibiotic. Variables selected by forward and backward approaches for the base model included foreign, possession of non-prescribed antibiotics, and gender. Two interaction terms, gender by possession of non-prescribed antibiotics and foreign by possession of non-prescribed antibiotics, added significantly to the model, but these interaction terms violated the assumption of sampling adequacy and were, therefore, not added to the final model. Potential confounding variables, including higher education, age, season, rural residence, health region, and empirical treatment with a fluoroquinolone, were tested for their effects on base model variables. There was evidence of age confounding the effect of gender, therfore age was added to the base model. None of the other variables listed had a confounding effect.

Four outliers of the final model were identified (standardized residuals for outliers were >3·29 or <−3·29). Final model results, following removal of the outliers, are given in Table 5. With inverse probability weighting for season applied to the data, the changes in coefficients for foreign, possession of non-prescribed antibiotic, and gender were <8%, but changes for two of the oldest age quartiles were >10%.

Study validity

Examination of a sample of eligible Calgary Health Region patients who were not asked to participate or who were asked but chose not to participate showed that the ciprofloxacin-resistance rate was less among non-participants (26·1%, $n=161$) than among Calgary study participants (33·9%, $n=165$; $\chi^2=46·5$, $P<0·001$). Among the non-participants in the Calgary Health Region, 19·9% acquired infection in a foreign country, and the crude univariate $OR_{foreign}$ was lower for Calgary non-participants (OR 2·0, 95% CI 0·9–4·5) than for participants in this region (OR 44·3, 95% CI 17·2–114·1). We translated the participation bias effect into a bias-corrected multivariable OR value for foreign travel for the full dataset (we assumed the effect measured was not unique to the Calgary Health Region and would also apply to the Chinook Health Region). The calculated the participation bias factor [equation (1)] as 4·8,

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Table 3. *Univariate analyses of risk factors for ciprofloxacin resistance of* Campylobacter *strains. Data collected from reported* Campylobacter *infections in southern Alberta, 1 February 2004–29 July 2005* (*n* = *210*)

	Cases		Adjusted†	
Variable‡	Resistance (%)	*n*	OR	95% CI (OR)
Foreign	77·9	68	38·5***	14·9–99·6
Macro-region				
Latin America	76·5	34	28·2***	9·1–87·8
Asia	90·5	21	137·7***	23·9–792·9
Europe	50·0	10	10·9**	2·2–53·3
Possession of non-prescribed antibiotics	64·3	14	4·8*	1·3–17·1

OR, Odds ratio; CI, confidence interval.
† Adjusted for age, sex, higher education, health region, rural residence, and season.
‡ Refer to Table 1 for variable descriptions.
* $P<0·05$, ** $P<0·01$, *** $P<0·001$.

Table 4. *Univariate analyses of risk factors for ciprofloxacin resistance of* Campylobacter *strains from reported* Campylobacter *infections in southern Alberta, 1 February 2004–31 January 2005* (*n* = *133*)

	Cases		Adjusted†	
Variable‡	Resistance (%)	*n*	OR	95% CI (OR)
Foreign	75·0	42	34·4***	9·4–126·3
Possession of non-prescribed antibiotics	62·5	8	5·7*	1·0–33·7

OR, Odds ratio; CI, confidence interval.
† Adjusted for age, sex, higher education, health region, rural residence, and season.
‡ Refer to Table 1 for variable descriptions.
* $P<0·05$, *** $P<0·001$.

Table 5. *Risk factors for ciprofloxacin resistance identified from multivariable logistic regression model of reported* Campylobacter *infections* (*N* = *205*) *in southern Alberta, 1 February 2004–29 July 2005*

Variable*	*P* value†	OR	95% CI (OR)
Foreign	<0·001	93·2	29·6–292·9
Possession of non-prescribed antibiotics	0·005	13·3	2·2–80·9
Age (yr)	0·03		
28–37	0·02	0·2	0·04–0·8
38–49	1·0	1·0	0·3–4·1
⩾50	0·03	0·2	0·04–0·9

OR, Odds ratio; CI, confidence interval.
* Refer to Table 1 for variable descriptions.
† Significance of the logistic regression Wald statistic.

so the $OR_{foreign}$ adjusted for participation bias was estimated as 93·2/4·8 = 19·4.

We evaluated the potential effect of differential misclassification of resistance on the model caused by the use of a surrogate ciprofloxacin susceptibility testing method in the Calgary region. Gaudreau & Gilbert [19] found nalidixic acid diffusion testing had a sensitivity of 100% and specificity of 98·5%, with respect to the gold standard test for ciprofloxacin susceptibility (agar dilution). Based on these values and the Calgary data, the estimated number of correctly classified ciprofloxacin-resistant *Campylobacter* strains in the Calgary sample was 54 [equation (2)]. This suggested that two of the 56 Calgary infections assumed to be ciprofloxacin resistant may have been misclassified. Ten copies of the original dataset were altered by imputing ciprofloxacin susceptibility for two randomly selected participants with resistant *Campylobacter* from the Calgary region patients.

Potential misclassification may have biased the original OR estimates both away from and towards the null. With the altered datasets, the average multivariable OR for foreign travel (86·9) was 7% less than it was with the original dataset (93·2) and the average multivariable OR for possession of non-prescribed antibiotics (14·6) was 10% greater with the altered datasets than it was with the original dataset (13·3). Foreign travel was a significant risk factor for

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resistance with the ten altered datasets, and possession of non-prescribed antibiotics was a significant risk factor with nine of the ten altered datasets. It appears, then, from these simulated datasets in which misclassification was taken into account, the conclusions from the final model were robust against effects of misclassification.

DISCUSSION

The proportion of ciprofloxacin resistance among the *Campylobacter* strains involved in this study (31·0%) falls between levels reported within the past 5 years in Alberta and Quebec, which range from 2% to 47% [2, 20, 21]. Similar to other reports [20, 22], the levels of resistance in *C. coli* was higher than in *C. jejuni*.

This case-control study examined a large number of hypothesized risk factors for ciprofloxacin resistance in *Campylobacter* infections. The effect of foreign travel has been discussed in many observational studies of antibiotic resistance in *Campylobacter* infections [7–10, 23, 24]. Our data showed foreign travel dominated any other risk factors that were examined. Furthermore, stratification of the data by regional group was important because it allowed a more detailed understanding of the risk associated with foreign travel. Cases were almost 140 times more likely than controls to have an infection acquired in Asia, but only 11 times more likely to have an infection acquired in Europe. A larger study with finer geographic groupings (e.g. by country) would probably have allowed us to capture a wide range of risk levels within macro-regions.

It has been shown that *Campylobacter* are able to develop high levels of resistance to fluoroquinolones soon after exposure [25, 26], and in a previous case-control study, quinolone use appears to increase risk of quinolone resistance in *Campylobacter* infections in humans [10]. In this study, 10·8% of cases and 2·8% of controls reported empirical treatment with a fluoroquinolone; however, we could not demonstrate that this was a risk factor for ciprofloxacin resistance.

Self-medicating with antibiotics does occur, and studies report levels of leftover antibiotic possession range between 9% and 38% [27, 28]. While antibiotic self-medication is important and often effective in the prevention and treatment of travellers' diarrhoea [29], and while possession of leftover antibiotics may be due to oversized packaging, i.e. not always due to incomplete courses of previous treatments [30], the potential for incorrect self-medication with non-prescribed antibiotics to contribute to bacterial resistance is a great concern [28, 31]. We agree with McNulty *et al*. [30], who suggest that the use of antibiotics may not align with prescribing data, and that this could affect the results of epidemiological studies such as ours.

We ascribed the potential for self-medicating to those who answered 'yes' to: 'Do you have any antibiotics that you would use future illness?' In our study, possession of non-prescribed antibiotics, which was reported by 6·7% participants ($n=210$), independently contributed to the likelihood of resistance. Possession was also the only risk factor identified in domestically acquired infections; further demonstrating its distinct effect in the absence of travel. Unfortunately, we did not ask participants who reported possession of non-prescribed antibiotics if they used them. Although 78·6% of those who had non-prescribed antibiotics ($n=14$) reported that they used an antibiotic for their *Campylobacter* illness, it is unclear if this was prescribed or non-prescribed use. Furthermore, we could not determine if any non-prescribed antibiotics were taken prior to submitting a stool sample (empirical treatment). Future studies with a larger sample size and higher exposure numbers, as well as more detailed questions on this topic could help to clarify this issue.

In our study, we collected food consumption data in units of typical consumption frequency over a 2-week period, rather than positive/negative consumption prior to onset. Compared to dichotomous consumption data, frequency data allowed for greater discrimination in risk estimates. For example, if chicken consumption was categorized as never/ever the univariate model for resistance would have a β-coefficient standard error of 0·72, while the model using the categorized frequency data had a standard error of 0·18. Nevertheless, unlike others [23], we found that those who consume chicken frequently were not more likely to have *Campylobacter* infections with ciprofloxacin resistance than were those who consume chicken infrequently. Compared to estimates of quinolone and fluoroquinolone resistance among *Campylobacter* isolated in retail chicken from other countries [32, 33], Canadian estimates of resistance are low, ranging from 1% to 12% [20, 34, 35]. Potentially, low prevalence of resistance in *Campylobacter* in chicken may have been a reason behind the lack of risk associated with chicken consumption here. Others have found swimming also contributed to nalidixic acid resistance risk in *Campylobacter* infections [7], but

we did not find consumption of untreated water, including unintentional consumption while swimming, to be an important risk factor.

We also investigated work-related potential risk factors. Others have found nalidixic acid resistance to be higher in faecal bacteria of livestock workers than in those of non-agricultural workers [36]. The proportion of participants in this study who handle animals as part of their occupation was higher than the proportion in the provincial workforce (2·4%) [37], but this type of work was not associated with ciprofloxacin resistance.

The need to examine the role of home cleaning and personal use of antibacterial products in the development of infections from antibiotic-resistant organisms has recently been advanced by several authors [15, 38, 39]. In the present study, the use of antibacterial dish soap and a brand of toothpaste known to contain triclosan, an agent that may be involved in the development of antibiotic cross-resistance, were not found to be associated with resistance. The quality of the data and the validity of these findings may be questionable, since a high proportion of participants, 54% and 29%, respectively, reported using these products. Given the number of dish-soap products and toothpaste brands available, it is seems probable that the frequency of reported use is greater than that of true use. Sensing that the use of antibacterial dish soap is an indication of good hygiene, participants may have been more likely to answer 'yes', and the quality of recall of product details among most people is probably modest. A cohort format may be a more suitable than a case-control format to examine the effects of these products on the likelihood of antibiotic resistance.

Other potential shortcomings of this study include the fact that some participants were not blinded to their antibiotic resistance status, which may have introduced a degree of recall bias. Unexpectedly, 37 participants (17·9%, $n=207$) reported that they knew the results of the antibiotic susceptibility testing conducted on their *Campylobacter* strain. More than half of those (56·8%) had resistant strains, and this may have affected the way they answered questions regarding exposures to antibacterials and antibiotics.

Participation bias, an increasingly formidable challenge to overcome in observational studies [40], can involve more than one subset of the population. In our study, there was data missing from non-participants: people who could have, but did not participate and from non-submitters: people who were infected, but did not seek medical help or were not asked to submit a stool sample. We estimated the effect of non-participation on $OR_{foreign}$ and it was considerable. Markedly, among non-participants in the Calgary Health Region, $OR_{foreign}$ was not significant. It is unclear from the data why the effect of travel on resistance was so small among non-participants, but it is possible that, in contrast to participants, non-participants, who were more commonly infected with domestically acquired and ciprofloxacin-susceptible strains, had infections that were more easily treated, and or, shorter in duration and were, therefore, more active at the time of interview and had less time to answer the questionnaire. We therefore suspect that the true effect of travel was less than we have reported. Nevertheless, given the magnitude of the estimated risk, travel was still likely to be a significant factor.

Unfortunately, we had no data to estimate the effect of non-submitters. The lack of data on non-reported intestinal disease, which this study, along with many others, suffers from, leads to results that describe only more severe diseases [41]. Furthermore, Tam *et al*. reported that physicians are more likely to ask for stool samples from those who recently travelled abroad [41]. If this applied to our study population, we can assume that our sample population included, relative to domestic infections, an oversampling of travel-related infections. However, this oversampling would not have biased our risk estimate for travel if the proportion of resistance in travellers and in domestically infected patients in our sample were the same as those in the study population.

Nalidixic acid susceptibility testing is an effective tool for screening fluoroquinolone susceptibility in enteric pathogens [19]. We were satisfied that the Calgary Health Region resistance data was not a source of differential misclassification as the OR estimates for foreign travel and possession of non-prescribed antibiotics were stable in our sensitivity analysis.

In conclusion, results from this case-control study demonstrate the overwhelming influence of foreign travel on the likelihood of fluoroquinolone resistance among *Campylobacter* infections in southern Alberta, and the possibility that individuals who have personal reserves of antibiotics may, through self-medication, be more likely to be infected with a resistant strain. Increasing frequency of chicken consumption was not a significant risk factor for resistance. A larger study is required to more conclusively test the effects of possession of non-prescribed antibiotics and

empirical treatment with a fluoroquinolone, which are uncommon in the population.

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DECLARATION OF INTEREST

None.

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