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Risk factors associated with antibiotic prescriptions for cases of enteric pathogens in Canada, 2015–2019

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Abstract

Inappropriate antibiotic use is a key driver of antibiotic resistance and one that can be mitigated through stewardship. A better understanding of current prescribing practices is needed to develop successful stewardship efforts. This study aims to identify factors that are associated with human cases of enteric illness receiving an antibiotic prescription. Cases of laboratory-confirmed enteric illness reported to the FoodNet Canada surveillance system between 2015 and 2019 were the subjects of this study. Laboratory data were combined with self-reported data collected from an enhanced case questionnaire that included demographic data, illness duration and symptoms, and antibiotic prescribing. The data were used to build univariable logistic regression models and a multivariable logistic regression model to explore what factors were associated with a case receiving an antibiotic prescription. The final multivariable model identified several factors as being significantly associated with cases being prescribed an antibiotic. Some of the identified associations indicate that current antibiotic prescribing practices include a substantial level of inappropriate use. This study provides evidence that antibiotic stewardship initiatives targeting infectious diarrhoea are needed to optimize antibiotic use and combat the rise of antibiotic resistance.

Introduction

Antibiotics are a critically important medical therapy, but inappropriate antibiotic use is a major public health concern. Antibiotic use contributes to the ongoing rise of antibiotic-resistant organisms at the population level and can result in a multitude of adverse health outcomes for individual cases [1–3]. Antibiotics are not generally recommended for cases of enteric illness in otherwise healthy individuals, as the illness is typically short in duration and self-limiting (Todd F Hatchette and Dana Farina [4, 5]). Despite this, there is growing evidence that a substantial proportion of enteric illness cases in Canada receive an antibiotic [6, 7].

Inappropriate antibiotic use can be detrimental in cases of enteric illness as it can increase the risk of developing hemolytic–uremic syndrome (HUS) in cases whose illness is caused by Shiga-toxin producing *Escherichia coli* (STEC) [8]. It can also increase the likelihood of bacteriological relapse as well as reinfection in cases of non-typhoidal salmonellosis [9, 10]. These risks are in addition to other generic risks of antibiotic use such as antibiotic-associated diarrhoea and development of *Clostridium difficile* infection [11, 12].

Enteric illness causes approximately eight million illnesses in Canada every year, with over 19,000 cases requiring hospitalization, and approximately 270 resulting in death [13, 14]. Antibiotic prescribing practices for enteric illness are poorly understood in Canada. The Public Health Agency of Canada's Human Antimicrobial Use Report, using data from the Canadian Disease and Therapeutic Index, reported that in 2014, 5.3% of diagnoses of 'disease of the gastrointestinal system' had an antimicrobial recommended [7]. This broad category included enteric illness, as well as a multitude of other diseases. In a study that specifically examined laboratory-confirmed cases of bacterial enteric illnesses in three sentinel sites across Canada, 49.3% of cases received an antibiotic [6]. However, it is unclear whether this level of use was appropriate and justified by treatment guidelines as such a determination requires a deeper exploration of case characteristics.

Treatment guidelines generally state that antibiotic therapy is not recommended for enteric illness unless specific factors are present, such as if the case has a recent history of international travel, is immunocompromised, or is of very young or old age [15]. Antibiotic therapy may also be

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more advantageous if the case presents with fever and bloody diarrhoea or has been ill for more than a week [16, 17].

The causative pathogen of the illness can also determine whether antibiotic therapy is recommended. Guidelines indicate that for some pathogens, such as *Giardia* spp. or *Shigella* spp., antibiotics are generally beneficial and routinely recommended [15]. In contrast, if STEC is the causative agent, antibiotic use is contraindicated in all cases [16, 17]. Other pathogens fall somewhere in between, where antibiotics may be recommended for some scenarios. It is important to note that the causative pathogen is difficult to ascertain when a case first presents with symptoms. It can take several days to obtain the results of stool testing, and there are situations where obtaining a stool sample may not even be possible [4]. When antibiotic treatment is initiated prior to determining the causative agent, it is referred to as empiric treatment and is generally not recommended by treatment guidelines for cases of acute diarrhoea [16, 17].

It is currently not clear that to what extent antibiotic prescribing practices for enteric illness are in concordance with treatment guidelines in Canada. Knowledge pertaining to factors associated with antibiotic prescribing can inform the design and implementation of future stewardship interventions. The objective of this study was to explore the factors associated with antibiotic prescribing in laboratory-confirmed cases of enteric illness reported to the FoodNet Canada surveillance system. We then discuss how the factors associated with antibiotic prescribing are in concordance with treatment guidelines utilized by Canadian healthcare practitioners.

Methods

Study design and setting

Cases of laboratory-confirmed enteric illness reported to the FoodNet Canada surveillance system during the five-year span from 1 January 2015 to 31 December 2019 were the subjects of this study. During the study period, FoodNet Canada operated three sentinel sites located in Fraser Health in British Columbia; Alberta Health Services Calgary and Central Zones in Alberta; and the Middlesex--London Health Unit in Ontario. In July 2019, FoodNet Canada launched a new sentinel site located in the Centre intégré de santé et de services sociaux (CISSS) de la Montérégie-Centre in Québec, but data from this site were not included in this study. Cases reported to FoodNet Canada prior to the study period were excluded from the analysis as 2015 was the first full year that FoodNet Canada comprised of all three sentinel sites. This decision was made to mitigate potential biases that could arise from temporal or spatial inconsistencies.

Data source

FoodNet Canada is a comprehensive sentinel site surveillance system that supports efforts to reduce the burden of enteric diseases in Canada [18]. The surveillance system is coordinated by the Public Health Agency of Canada in collaboration with provincial and local public health authorities. To be included in this passive surveillance system, a case must present to a healthcare practitioner, who would then need to request a specimen sample, and then submit that sample to a hospital or private medical laboratory to test for enteric pathogens. Positive isolation of a pathogen is reported directly to the healthcare practitioner and the local public health authority. The local public health authority then administers an enhanced standardized questionnaire for enteric diseases to the cases with positive isolation of an enteric pathogen. The responses to the questionnaire are sent to FoodNet Canada for data cleaning and analysis. Cases determined to be lost to follow-up were excluded from the analysis.

Variables

The outcome of interest in this study was prescription of one or more antimicrobials to patients with laboratory-confirmed enteric illness. This variable was measured by cases' response to the question: 'Were you prescribed any antibiotics for this infection?'. The illnesses included in this study were campylobacteriosis, cryptosporidiosis, cyclosporiasis, giardiasis, salmonellosis, shigellosis, STEC infection, and yersiniosis. Case definitions for these diseases were based on provincial standards and are summarized in Supplementary Material S1.

The demographic factors analysed were age, gender (due to data limitations, this variable was binary), and recent history of international travel. Treatment guidelines indicate that for some enteric pathogens, cases that are very young (<1 year) or elderly (≥65 years) have an increased risk of developing severe disease and subsequently may require antibiotic therapy [16, 17]. We therefore grouped age into seven categories: <1, 1-4, 5-19, 20-34, 35-49, 50-64, aunivariable analyses are inclund ≥65 years old. A recent history of international travel was defined as any travel outside of Canada other than the United States during the incubation period of the pathogen (list of incubation periods by pathogen can be found in Supplementary Material S1).

The questionnaire was reviewed *a priori* to identify what demographic, illness-related, and setting-level factors could be analysed to examine their associations with antibiotic prescribing. In total, 23 factors directly related to the illness were analysed for their association with antibiotic prescribing. Eighteen of these were self-reported presence of signs and symptoms. The duration of illness was calculated for cases that reported both an onset of illness date and a recovery date. We then categorized these cases into the groups 'ill for one week or less' and 'ill for greater than one week'. For cases who reported an onset date but were interviewed prior to symptoms resolving, we calculated the number of days between onset and interview date. We subsequently categorized these cases in a similar fashion with the groups being 'still ill for one week or less' and 'still ill for greater than one week'. These four categories were combined into the single 'duration of illness' variable. We also explored whether self-reported hospitalization, visit to an emergency room, source of the isolate (stool, blood, urine, or other), or causative pathogen were associated with receiving an antibiotic prescription.

We were also interested in examining whether there was an association between antibiotic prescribing and the setting of a case, in both time and place. We therefore included the variables year of onset and season of onset (as defined by astrological date; e.g. winter was from December 21 to March 20) in our analysis to explore temporal associations to antibiotic prescribing. To explore geographic associations, we included the sentinel site the case was from and if the case lived in a rural or urban location as variables. To determine urban or rural status, we cross-referenced the city or county of residence reported by cases with Statistics Canada classifications of population centres [19]. Cases residing in large urban population centres (population of 100,000 or more) were classified as 'urban', and all others were classified as 'rural'.

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Statistical analysis

Univariable logistic regression models were developed to screen for variables that were associated with a case receiving an antibiotic prescription. All variables that were statistically significant at a relaxed significance of α=0.2 in the univariable models were initially explored in the multivariable logistic model. We then used a hypothesis testing model building procedure to produce a model that best fit the data, including removing the non-significant ($P > 0.05$) variables. Variables with ≥3 categories were assessed using the likelihood ratio test. As non-statistically significant variables were removed from the model, we evaluated the impact on the remaining significant variables to detect potential statistical confounding. If removing a variable resulted in a ≥30% change in the coefficient or standard error of a significant variable, the variable was identified as a confounding variable and reintroduced into the model. All statistically significant and confounding variables in the model were tested for significant interaction ($P < 0.05$) with gender or age category. Those interactions found to be statistically significant ($P < 0.05$) were included in the final model. Variables included in the final model were examined for multicollinearity by calculating generalized variance inflation factor, where a value of >5 was deemed concerning for multicollinearity. A Hosmer–Lemeshow goodness-of-fit test was performed on the final multivariable model. Model diagnostics were then conducted on the final model to identify extreme observations and highly influential covariate patterns. The model was then rerun with the identified extreme observations, and highly influential covariate patterns were removed to assess the effect on the model coefficients. The statistical analysis for this study was conducted using Stata® 14 for Windows (Stata Corporation, College Station, TX). The data used in this study were collected as part of the FoodNet Canada surveillance system. Secondary analysis using de-identified data is covered as part of the memorandums of agreement between FoodNet Canada and contributing sentinel sites.

Results

Over the study period, a total of 7,796 laboratory-confirmed cases were reported to FoodNet Canada. Of these cases, 795 were lost to follow-up and were not included in the analysis. The antibiotic prescribing status for 128 cases was not known, so these were also excluded from the analysis. Additionally, four cases were missing data for other variables and were excluded. The number of cases varied from 1,253 cases in 2015 to 1,478 cases in 2019. Cases ranged in age from 1 month to 98 years old, with an average age of 35 years old. *Campylobacter* was the most diagnosed cause of illness (36.3%), followed by *Salmonella* (29.8%) and *Giardia* (13.2%) (Table 1). Antibiotics were prescribed to 3,479 of the 6,869 (50.6%) laboratory-confirmed cases included in this analysis (Table 1). Of the pathogens included in this analysis, cases with infections of Cyclospora had the highest rate of antibiotic prescribing (75.8%) and STEC had the lowest rate (18.9%).

Table 1. The number of cases by causative pathogen with the number and proportion that received an antibiotic prescription in cases reported to FoodNet Canada, 2015–2019

Causative pathogen	Frequency	Number receiving an antibiotic prescription (proportion)
Campylobacter	2,495	1410 (56.5%)
Salmonella	2,046	1004 (49.1%)
Giardia	910	570 (62.6%)
Yersinia	391	147 (37.6%)
STEC	407	77 (18.9%)
Cryptosporidium	353	101 (28.6%)
Shigella	205	123 (60.0%)
Cyclospora	62	47 (75.8%)
Total	6869	3479 (50.6%)

The results of the univariable analyses are included in Supplementary Material S2. In total, 24 factors were associated with antibiotic prescribing at the liberal P-value threshold of less than 0.2 and were therefore explored in the multivariable model building process. The final best-fit multivariable model included 15 variables. The factors that were associated with significantly higher odds of receiving an antibiotic prescription were as follows: being of older age; being male (only in domestic cases); recent international travel (only in males); being ill for a week or more; experiencing abdominal bloating, chills, diarrhoea, or nausea; not experiencing abdominal pain; visiting the emergency room; being admitted to hospital; having the pathogen be isolated from blood or urine; having an illness onset in the early years of this study; and being reported to sentinel site X (Table 2). Causative pathogen was also significantly associated with antibiotic prescribing. The pathogens *Campylobacter, Cyclospora, Giardia, Shigella*, and *Yersinia* were found to have significantly higher odds than *Salmonella*, the selected referent pathogen. *Cryptosporidium* and STEC had significantly lower odds than *Salmonella.* No variables were included as confounders, and there was a significant interaction between gender and international travel. All variables included in the final model had a generalized variation inflation factor of <1.3. The Hosmer–Lemeshow goodness-of-fit test was not significant ($P = 0.703$), indicating that the model fits the data. No observations or covariate patterns were identified with a large measure of influence whose removal changed the interpretation of the final model.

Discussion

This work provides an exploratory analysis of factors associated with antibiotic prescribing in cases of enteric illnesses in Canada. Over half of the laboratory-confirmed cases of enteric illness included in this study received an antibiotic prescription. Our analysis showed various demographic, agent, symptom, treatment, and geographic factors to be significantly associated with antibiotic prescribing.

There is substantial discordance when comparing the factors associated with prescribing identified in this study with treatment guidelines for enteric illness. There are several factors, including recent history of international travel, extra-intestinal infection (source of isolate), prolonged duration of illness, and hospitalization, where there is congruity between guidelines and observed practice [16, 17]. However, other associations identified in this study either contradicted guideline recommendations or were not mentioned in guidelines at all (factors such as gender, sentinel site, year, and some symptoms). This suggests that there may be a considerable amount of inappropriate antibiotic use in laboratory-confirmed cases of enteric illness and that antibiotic prescribing decisions may be influenced by factors outside of the realm of clinical significance. Examples of such factors outside the realm of clinical significance could include patient expectations (or perceived expectations) and

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Table 2. Odds ratios and *P*-values for the final best-fit multivariable model identifying factors associated with laboratory-confirmed cases of enteric illness reported to FoodNet Canada being prescribed an antibiotic, 2015–2019

Variable	Level	OR	95% CI	*P*-value
Year	2015	Referent		
	2016	1.03	0.84–1.27	0.749
	2017	1.08	0.88–1.33	0.475
	2018	0.95	0.77–1.16	0.586
	2019	0.80	0.66–0.98	0.029
Site	Site X	1.38	1.14–1.67	0.001
	Site Y	0.57	0.49–0.67	<0.001
	Site Z	Referent		
Age category	<12 months	0.94	0.40–2.23	0.892
	1 to 4 years	0.57	0.42–0.77	<0.001
	5 to 19 years	0.57	0.45–0.71	<0.001
	20 to 34 years	0.78	0.65–0.95	0.012
	35 to 49 years	Referent		
	50 to 64 years	1.24	1.01–1.52	0.042
	65+ years	0.92	0.72–1.17	0.483
Gender	Female (no travel)	Referent		
	Male (no travel)	0.76	0.65–0.89	0.001
	Female (travel)	Referent		
	Male (travel)	1.13	0.91–1.42	0.271
International travel	No (female)	Referent		
	Yes (female)	1.18	0.97–1.45	0.101
	No (male)	Referent		
	Yes (male)	1.76	1.45–2.15	<0.001
Causative pathogen	*Campylobacter*	1.89	1.60–2.22	<0.001
	Cryptosporidium	0.54	0.40–0.74	<0.001
	Cyclospora	3.32	1.69–6.53	<0.001
	Giardia	3.53	2.77–4.5	<0.001
	Salmonella	Referent		
	Shigella	1.88	1.28–2.76	0.001
	STEC	0.40	0.28–0.57	<0.001
	Yersinia	1.60	1.16–2.19	0.004
Duration of illness	<=1 week	Referent		
	>1week	1.47	1.19–1.8	<0.001
	Still ill <=1 week	1.02	0.80–1.31	0.861
	Still ill >1week	1.33	1.10–1.61	0.004
Source of isolate	Blood	11.53	5.14–25.89	<0.001
	Stool	Referent		
	Urine	16.08	6.73–38.41	<0.001
	Other	1.01	0.20–5.01	0.989
Abdominal pain	No	Referent		
	Yes	0.82	0.68–0.99	0.036
Abdominal bloating	No	Referent		
	Yes	1.22	1.05–1.41	0.008
Chills	No	Referent		
	Yes	1.26	1.08–1.46	0.003
Diarrhoea	No	Referent		
	Yes	1.70	1.26–2.28	<0.001
Nausea	No	Referent		
	Yes	1.32	1.14–1.52	<0.001
ER visit	No	Referent		
	Yes	1.47	1.27–1.71	<0.001
Hospitalization	No	Referent		
	Yes	2.23	1.70–2.94	<0.001

concerns about the financial burden of the disease such as lack of access to paid sick leave [20, 21].

The significant difference in prescribing practices observed between sentinel sites in this study is intriguing. There are many factors that could contribute to this observed geographic variation, including differences in the health systems, physician practices and incentives, or patient populations. As our multivariable model included several patient-level factors such as age and still found a significant association between antibiotic prescribing and sentinel site, it is unlikely that these patient-level factors were the underlying cause of geographic variation. Geographic variation in the rates of antimicrobial consumption in Canada has been previously observed. In their 2022 report, the Canadian Antimicrobial Resistance Surveillance System also described geographical variation in antimicrobial consumption rates across the provinces and territories in Canada [22]. Further investigation of this geographic variation could provide valuable insight for stewardship campaigns if the factors contributing to lower prescribing rates could be replicated in higher prescribing areas.

Gender was another factor associated with antibiotic prescribing in this study but lacked any mention in treatment guidelines. Previous studies have found females were prescribed antibiotics more often than their male counterparts, which is similar to our study [23] [24]. Our finding that the association between gender and antibiotic prescribing was dependent on recent international travel history has not been described in the literature, to the best of our knowledge. A postulated rationale to explain the variation in prescribing rates points towards differences in social and behavioural factors among genders as a possible rationale for prescribing variation [25]. Understanding if, and subsequently how, these factors are involved in antibiotic prescribing decisions would provide critical information for stewardship efforts.

A question identified by the research team entering this study was what proportion of cases received empiric antibiotic therapy versus culture-driven therapy. The available data could not directly answer this question because the temporal order of when antibiotics were prescribed and when causative pathogen was identified could not be established. However, the observed association between antibiotic use and causative pathogen provides valuable insight into this question. Our study found that there were significant differences in the prescribing rates observed between the causative pathogens, even when controlling for signs

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of severe infection such as fever or duration of illness. This suggests that at least a proportion of cases were likely prescribed antibiotics based on diagnostic testing. On the other hand, our study also observed that 19% of STEC cases received an antibiotic, a practice that is contraindicated by treatment guidelines as antibiotic therapy has been shown to increase the odds of developing HUS in cases of STEC [8]. It is probable that the STEC cases in our study that received an antibiotic prescription were treated empirically. The finding that one in six cases of STEC received an antibiotic prescription is highly concerning and illustrates a significant risk of empirically prescribing antibiotics for enteric illness. Our results show evidence that both empiric and culture-driven antibiotic therapies are being used to treat cases of enteric illness. Further research is needed to understand this aspect of antibiotic prescribing practices better.

Our study was restricted to examining the antibiotic prescribing practices in laboratory-confirmed cases of enteric illness reported to three sentinel sites across Canada. Laboratory-confirmed cases represent just a fraction of the cases of enteric illness that exist in the community [14]. The laboratory-confirmed cases likely do represent the group that is most likely to receive an antibiotic, but cases could seek medical care and receive an antibiotic without submitting a specimen sample or having the specimen sample test positive. The antibiotic use and prescribing practices for non-laboratory-confirmed cases are likely different. In addition, our finding that antibiotic prescribing practices varied geographically between the three sentinel sites also limits the external generalizability of our results. The associations observed in our study have provided valuable insight into prescribing practices in our sample population, but further research is needed to understand the broader picture of antibiotic use in enteric illness cases. Future studies should aim to explore the prevalence of antibiotic prescribing in cases that are not captured by laboratory-based surveillance, as this would provide a more comprehensive understanding of antibiotic use for enteric illnesses. Analysing primary care electronic medical records could be a viable approach for this purpose.

In conclusion, our study found that several factors are associated with antibiotic prescribing in cases of enteric illness, with some associations lacking a clinical rationale that can be found in treatment guidelines. These findings suggest that current antibiotic prescribing practices are not concordant with treatment guidelines and that a substantial level of inappropriate use exists. This provides evidence that antibiotic stewardship initiatives in the community specifically targeting enteric illness are needed to optimize antibiotic use and combat the rise of antibiotic resistance. These stewardship initiatives need to also consider the upstream drivers of antibiotic prescribing.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0950268824001365.

Data availability statement. If interested in accessing data or other materials related to this manuscript, readers may contact the corresponding author.

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