Characterization and Prediction of Multiple Episodes of Different Reportable Diseases in Montreal Residents, 1990-2012.

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Abstract

Studies of public health reporting have examined multiple episodes of the same communicable disease within an individual, but have not described multiple episodes of *different* reportable diseases within individuals. Such an analysis could identify ways in which to prevent consecutive reportable disease episodes and could guide future revisions to public health intervention strategies. Using passive surveillance data, an exploratory analysis of Montreal residents with multiple reportable disease episodes from 1990 to 2012 was conducted. During this time, there were 157,839 individuals with at least one disease report and a total of 179,455 reportable disease episodes. Individuals with more than one communicable disease episode accounted for one of every five communicable disease reports, were more likely to have sexually transmitted infections (STIs) and were more likely to reside in the neighbourhood encompassing Montreal's gay village. Enteric diseases, as a group, were reported at lower rates in persons with multiple episodes. However, amoebiasis, giardiasis and shigellosis were reported more commonly in men with multiple episodes than in men with only one episode. This finding supports the mounting evidence that enteric diseases may be sexually transmitted, especially among men who have sex with men. Consequently, to aid public health authorities in identifying probable cases of sexually acquired enteric diseases, we developed a logistic regression model to predict the probability of acquiring a future STI in individuals with an enteric disease report. Our final prediction model accounted for the age, sex, residential location, history of STI episodes and type of enteric disease acquired. This model had an area under the receiver operating characteristic curve of 0.77 and had acceptable calibration. It follows

that this prediction model can be used to guide efforts to investigate and control reported cases of enteric diseases by public health officials.

Abrégé

Les études épidémiologiques portant sur la signalisation des maladies à déclaration obligatoire (MADO) sont réalisées en tenant compte que d'une MADO à la fois et n'ont jamais décrites de multiples épisodes de *différentes* MADO chez un même individu. Une analyse qui tiendrait compte de toutes les MADO pourrait identifier des stratégies servant à empêcher des MADO à répétition et pourrait guider de futurs changements apportés aux interventions de santé publique. Nous avons utilisé des données de surveillance pour réaliser une analyse exploratoire ayant pour but de décrire la situation épidémiologique chez les Montréalais faisant des MADO à répétition. Entre 1990 et 2012, 179,455 cas de MADO vécus par 157,839 individus ont été déclarés à la direction de santé publique de Montréal. Une MADO sur cinq ont été signalée chez les personnes ayant eu plus d'un épisode. Ces personnes étaient plus susceptibles d'avoir des infections transmissibles sexuellement et par le sang (ITSS) et d'habiter dans le quartier comprenant le village gai de Montréal. Les maladies entériques, en tant que groupe, ont été signalées moins souvent chez les personnes ayant de multiples épisodes. Par contre, l'amibiase, la giardiase et la shigellose étaient signalées plus fréquemment chez les hommes avec plus d'un épisode que chez les hommes avec un seul épisode. Cette observation ajoute à la panoplie d'analyses épidémiologiques qui démontrent que les maladies entériques peuvent être transmissibles par voie sexuelle, en particulier chez les hommes ayant des relations sexuelles avec des hommes. Pour aider les autorités de santé publique à identifier les cas probables de maladies entériques acquises par voie sexuelle, nous avons développé une régression logistique pour prédire la probabilité d'acquérir une ITSS parmi les personnes signalées pour une maladie entérique. Le modèle de prédiction ayant le plus grand pouvoir prédictif

était une régression logistique ayant comme prédicteurs âge, sexe, lieu de résidence, antécédents d'ITSS, ainsi que type de maladie entérique acquis. Ce modèle avait une aire sous la courbe de 0.77 et avait une calibration acceptable. Conséquemment, ce modèle de prédiction peut être utilisé pour guider les efforts d'enquête et de contrôle des maladies entériques.

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Preface

This thesis is comprised of two studies, which aim to describe individuals with multiple episodes of different reportable diseases. The first study is an exploratory analysis on Montreal residents with multiple reportable disease episodes. It estimates the frequency with which individuals are reported to public health officials for multiple episodes of communicable diseases and describes the characteristics of these individuals. The second study focuses on individuals with multiple reportable disease episodes who may have acquired enteric diseases through sexual transmission. This study aimed to build a model to predict the probability that an individual with an enteric disease report may acquire a sexually transmitted infection in the future.

Five chapters are included in this thesis. Chapter one, the introduction, includes the background, rationale and objectives set prior to the beginning of the analyses. Chapter two describes the purpose and uses of communicable disease surveillance and case investigations. Chapter three presents the methods and the results of the exploratory analysis. Chapter four outlines the methods and the results of the prediction model. (Chapters three and four are written in the form of manuscripts intended for submission to peer-reviewed journals and are formatted accordingly.) Finally, chapter five presents the overarching conclusions of the two studies.

This thesis follows the guidelines and requirements of a manuscript-based thesis at McGill University.

Contribution of Authors

As first author of the exploratory analysis and prediction model studies, I contributed to the conception and planning of their study designs, conducted and performed all steps of data processing and analyses, interpreted the results, wrote both manuscripts, and incorporated all necessary revisions. My thesis supervisor, Dr. David Buckeridge, supervised all stages of the research. He contributed to the conception of the study designs, provided considerable knowledge on the topic, generated stimulating discussions with regard to the results, and revised both manuscripts. Lucie Bédard, a member of my thesis supervisory committee, contributed to the conception of the study designs, provided thoughtful insight and feedback on the results and edited both manuscripts. Dr. Robert Allard, the second member of my thesis supervisory committee, contributed to the study design of the prediction model and helped interpret the results. Jérôme Latreille helped shape the objectives of both studies, contributed to the interpretation of the results of both studies and reviewed the exploratory analysis manuscript.

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List of Abbreviations

AIC: akaike information criterion

AIDS: acquired immunodeficiency syndrome

AUC: area under the receiver operating characteristic curve

CI: confidence interval

HIV: human immunodeficiency virus

ME: multiple episodes of reportable diseases

MSM: men who have sex with men

OE: one reportable disease episode

OR: odds ratio

P: p-value

PHD: public health department

SD: standard deviation

STI: sexually transmitted infection

CHAPTER ONE

INTRODUCTION

Background

Surveillance of communicable diseases allows public health officials to protect the health of the population by monitoring trends in disease incidence and identifying determinants of disease. The information produced by surveillance in turn guides the planning and implementation of health services aimed at preventing and reducing the spread of illness.

Rationale

Generally, a public health department (PHD) will determine which cases of communicable diseases to investigate based on guidelines to direct investigative efforts and interventions. However, very few, if any, investigation protocols consider an individual's number of prior reportable disease episodes. While many epidemiological studies have examined rates of public health reporting of the same organism in an individual, to the best of our knowledge, no study has described persons who have experienced multiple episodes of different types of reportable diseases. As such, many individuals with multiple episodes go unrecognized and, without a targeted public health intervention, remain at risk of continuing to acquire and transmit further communicable diseases. A study to characterize the reporting of multiple episodes of reportable diseases in the same individual could guide revisions to public health intervention strategies by

providing a description of these individuals and suggesting ways in which to investigate their communicable disease episodes.

Objectives

The objectives of this thesis were:

1) To perform an exploratory analysis of Montreal residents with multiple episodes of different reportable diseases:
    A) To describe the frequency of multiple episodes of reportable diseases within a same individual;
    B) To determine the specific communicable diseases more commonly reported in subjects with more than one episode;
    C) To identify potential public health strategies to prevent multiple reportable disease episodes;
2) To provide public health officials with a method for identifying potential cases of sexually acquired enteric diseases (an occurrence common in persons with multiple reportable disease episodes):
    A) To build a prediction model capable of identifying Montreal residents with an enteric disease report who are at risk of acquiring a future sexually transmitted infection.

Chapter Two

Public Health Surveillance of Communicable Diseases

2.1 The purpose and uses of communicable disease surveillance

Public health surveillance is defined as the "[s]ystematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken" (Porta and International Epidemiological Association. 2008). Surveillance data are instrumental to public health officials, as they offer a quantitative approach to monitor the health of a given population and to identify any threats to its wellbeing. Accordingly, the information obtained through surveillance practices can direct and encourage timely public health control and prevention strategies (Thacker 2010).

In industrialized countries, a great amount of progress has been made to prevent and to treat communicable diseases. These efforts have resulted in a significant decline in communicable disease mortality. Nonetheless, continuous environmental and human behavioural changes, along with the evolving and adapting nature of infectious agents, may stimulate the appearance or re-appearance of communicable diseases. As a result, communicable diseases remain an important public health concern and persistent threat to developed countries (Pinheiro, Mathers et al. 2010). For this reason, it is imperative that public health authorities monitor trends in communicable diseases. As a result, surveillance of communicable diseases remains an important and integral task for public health officials (Van Beneden 2010).

Communicable disease surveillance allows public health authorities to monitor highly virulent diseases, identify new strains of antibiotic-resistant pathogens, track sources of contaminated food or water, and evaluate the effectiveness of public health control and prevention strategies (such as the efficacy and uptake of vaccination programs). It also aids in determining a baseline rate of disease, which enables public health officials to quantify the magnitude of a public health issue and detect communicable disease outbreaks. Ultimately, the main purpose of communicable disease surveillance is to direct rapid public health interventions and to plan the implementation of new public health measures by identifying current health issues and concerns (Public Health Agency of Canada 2009, Reintjes and Krickeberg 2010, Thacker 2010, Van Beneden 2010).

There exist many different types of communicable disease surveillance systems, which depend on various sources of information. These sources include household, school, workplace, and population registers, death certificates, health facility/physician records, health insurance records, laboratory records, and sentinel records. Among these sources, the most important are considered to be health facility/physician and laboratory records, as they are the foundation of mandatory communicable disease surveillance systems (Reintjes and Krickeberg 2010).

2.2 Mandatory communicable disease surveillance systems

Mandatory communicable disease surveillance systems are the most common form of infectious disease surveillance in local public health practice. This approach to surveillance is usually stipulated in law and supporting regulations, and is implemented as a population-based, passive surveillance program that requires doctors and/or laboratory

directors to report directly to local public health departments (PHDs) all incident cases of specified communicable diseases (Roush, Birkhead et al. 1999, Reintjes and Krickeberg 2010, Van Beneden 2010).

The communicable diseases for which reporting to public health officials is mandatory are termed reportable (or notifiable) diseases. They are defined by the Centers for Disease Control and Prevention as diseases "for which regular, frequent, and timely information regarding individual cases is considered necessary for [their] prevention and control" (Adams, Gallagher et al. 2013). The list of reportable diseases is continuously updated in order to best reflect public health officials' current priorities and concerns (Roush, Birkhead et al. 1999). (While reportable diseases can be either chemical or infectious in nature, this thesis focuses solely on *infectious* reportable diseases. Accordingly, all references to reportable diseases hereafter refer solely to *infectious* reportable diseases.)

The success of a reportable disease surveillance program depends on standardized case definitions, clear communication between clinicians, laboratories and PHDs, timely and complete reporting, as well as periodic assessments of its efficacy (Carter 1991, Public Health Agency of Canada 2009, Van Beneden 2010).

2.3 Public health surveillance of reportable diseases in Quebec, Canada

In Canada, provincial and territorial public health authorities determine which diseases are reportable in consultation with the Public Health Agency of Canada. Reportable diseases are generally classified into one of seven categories: enteric, food and waterborne diseases, diseases transmitted by respiratory routes, diseases transmitted by

direct contact and through the provision of healthcare, diseases preventable by routine vaccine, sexually transmitted and blood borne pathogens, vector borne and other zoonotic diseases and diseases under extreme surveillance (or potential bioterrorism agents) (Public Health Agency of Canada 2009).

Common case definitions for most notifiable diseases were agreed upon by the Canadian government along with provincial and territorial epidemiologists in 1991. These case definitions, which are updated on a regular basis, are used throughout Canada in order to ensure standardized reporting of confirmed, probable, possible and suspect cases of disease (Public Health Agency of Canada 2009).

In the province of Quebec, there are eighteen socio-sanitary regions, each with their own local PHD (Ministère de la santé et des services sociaux 2009). Public health reporting of notifiable diseases to a local PHD is required by law under the Public Health Act of Quebec. This act ensures the "maintenance and enhancement of the health and well-being of the general population" and calls for "ongoing surveillance of the health status of the population and of health determinants" (Government of Quebec 2001). It obliges diagnosing physicians and laboratory chief executive officers to report incident cases of reportable diseases to their regional PHD. A notifiable disease report must include a minimum set of information, including a patient's name, address, age, and sex (Government of Quebec 2001, Government of Quebec 2009). By requiring the transmission of personal information without patient consent, the provincial Public Health Act overrules patient/physician confidentiality. It is the ethical, legal and professional duty of public

health officials who obtain this personal information to ensure its confidentiality (Wong, Chernesky et al. 2008).

2.4 Case investigations of reportable diseases

While the collection of information obtained from each communicable disease report supports assessments of population health, the investigation of reported diseases allows for the identification of risk factors that can be modified to prevent the spread of illness in the population (Unité maladies infectieuses de la direction de santé publique de Montréal-Centre 2005). These case investigations can be initiated in both the presence and absence of a communicable disease outbreak.

2.4.1 Case investigations in the context of a communicable disease outbreak

A communicable disease outbreak occurs when the observed number of disease reports statistically surpasses the expected number of cases for a given time, place and/or population (Davis 2000, Reintjes and Zanuzdana 2010, Abubakar 2013). Outbreaks require immediate public health action in order to control them and to prevent the spread of further illness. Outbreak investigations are essential to achieving these goals (Reintjes and Zanuzdana 2010).

The main aim of an outbreak investigation is to identify the cause of the outbreak. This necessitates the collaboration of epidemiological, microbiological, toxicological and clinical experts. Moreover, outbreak studies can help describe new pathogens, provide further insight on existing diseases and influence future outbreak prevention guidelines (Service de protection de la santé publique - Direction de la santé communautaire 1992, Davis 2000, Reintjes and Zanuzdana 2010).

There are several steps involved in an outbreak investigation. Once an outbreak has been confirmed by public health authorities, it is imperative to establish a case definition in order to properly identify cases. Once these cases have been identified, officials can collect information on the affected individual's characteristics, the clinical manifestation of their infection and the presence of potential risk factors. This data is then analyzed with regards to time, place and person. Public health officials can then compare their hypotheses regarding the source or cause of the outbreak to the results of the epidemiological, laboratory and environmental data. Upon identifying a source for the outbreak, authorities can implement various control measures aiming to eliminate the source of the infection and to block the transmission of the disease. While these steps are key components of any outbreak investigation, they are not necessarily performed in a linear fashion. In fact, specific circumstances may require certain steps to occur simultaneously or skipped entirely (Reintjes and Zanuzdana 2010).

2.4.2 Case investigations in the absence of a communicable disease outbreak

Investigations of incident cases of disease by public health authorities are also important in the absence of an outbreak, as they serve as a preventative measure. For example, certain communicable diseases pose such an important health threat to the general population, that a single case may require immediate public health action (Carter 1991). Similarly, the investigation of certain sexually transmitted infections can help prevent adverse effects and complications with a person, and can also reduce the risk of transmission to other individuals (de la Boissière, Drapeau et al. 2004).

Ideally, case investigations of reportable diseases should be performed no later than 72 hours following the receipt of the communicable disease report by public health officials. These investigations are performed by public health nurses who administer disease-specific questionnaires to the patient and/or the patient's treating physician. These questionnaires aim to collect information on time, space and person/behavioural characteristics, while ensuring the standardized collection of data (de la Boissière, Drapeau et al. 2004). The information collected through these questionnaires supplements the patient data available in the initial communicable disease report and can help public health officials identify potential risk factors for disease (Unité maladies infectieuses de la direction de santé publique de Montréal-Centre 2005). Furthermore, case investigations provide public health officials with an opportunity to offer preventative counseling to the patient and to intervene on individuals who may not have been affected by a population-scale public health intervention effort (de la Boissière, Drapeau et al. 2004).

Depending on the reportable disease in question, case investigations permit public health officials: to explain the importance of adopting and maintaining safe sexual practices (such as reducing the number of sexual partners and using contraception); to offer instructions on the hygienic handling and manipulation of food; to suggest the procurement of a government-recommended vaccine; and to ensure that a doctor-prescribed treatment plan has been diligently followed and respected (de la Boissière, Drapeau et al. 2004).

Furthermore, case investigations allow public health authorities to identify and to treat, if necessary, individuals who have been in contact with the index-case and who may

have acquired the disease in question. In order to decrease their infectious period and their risk of transmitting the disease to others, public health officials can contact these individuals and suggest visiting a medical establishment where they can be screened for disease and receive proper care (de la Boissière, Drapeau et al. 2004).

While the benefits of case investigations are indisputable, limited resources and time restrictions make the investigation of all incident cases of reportable diseases unfeasible. As a result, every regional PHD must identify their own intervention priorities based on the reportable disease epidemiology in their population (de la Boissière, Drapeau et al. 2004). Despite each having their own outbreak and preventative investigation guidelines, it appears as though no PHDs follow a specific protocol to properly identify and investigate persons with multiple reportable disease episodes. The two epidemiological studies presented in the next two chapters of this thesis will help bridge this gap in public health case investigations.

Chapter Three

Characterization of Multiple Episodes of Different Reportable Diseases in Montreal Residents

The following manuscript outlines the methods and the results of an exploratory analysis which aimed to provide a broad overview of persons who have had multiple disease episodes reported to the Montreal PHD. The manuscript offers a general description of these individuals and envisions possible ways in which public health case investigations can be modified to better manage persons with multiple communicable disease episodes.

To the best of our knowledge, this is the first study of its kind to consider all the different communicable diseases which are reportable to public health officials. Seeing as this analysis is quite novel, only a brief background of the literature is provided at the beginning of the manuscript.

This manuscript was authored in collaboration with Lucie Bédard, Dr. David Buckeridge and Jérôme Latreille. We intend to submit this manuscript for publication to the American Journal of Public Health and have formatted the manuscript according to this journal's specifications.

Title: An Exploratory Analysis of Individuals with Multiple Episodes of Different Reportable Diseases, Montreal, 1990-2012.

ABSTRACT

Objectives. Studies of public health reporting have only examined multiple episodes of the same communicable disease within an individual. We aimed to characterize Montreal residents with multiple episodes of different types of reportable diseases from 1990 to 2012, while accounting for all reportable diseases.

Methods. We performed an exploratory analysis using descriptive statistics, contingency tables, graphics, and logistic regression.

Results. There were 157,839 individuals with at least one disease report and a total of 179,455 disease reports. The 9.8% of subjects with more than one episode accounted for 20.7% of all reported episodes. Subjects with multiple episodes were more likely to be reported for sexually transmitted infections than persons with only one episode [difference of proportions: 10.4% (95% CI: 10.0%-10.9%)] and to reside in the neighbourhood encompassing Montreal's gay village.

Conclusions. Individuals with multiple communicable disease reports place a large burden on public health officials. The results of this study may help guide investigation and prevention efforts.

Reportable disease surveillance is essential to detect and prevent the spread of communicable diseases in a population. It allows public health officials to monitor disease incidence, identify outbreaks in a timely manner, evaluate the performance of public health strategies and assess the need for interventions. As the epidemiology evolves, the list of reportable diseases is continuously updated in order to best respond to the public's needs and safety.[1] In Canada, as in the United States, it is mandatory that doctors and/or laboratories report incident cases of these diseases to their regional public health department (PHD).[2,3]

In addition to supporting efforts to control the transmission of disease, the reportable disease data collected through passive surveillance can also be used for scientific research. In particular, many epidemiological studies have used reportable disease data to examine the recurrence of disease in the same individual. The majority of these studies focused on estimating the incidence of, and describing the risk factors for, chlamydia,[4-10] and gonorrhea reinfection.[9-14] However, reportable disease data have also been used to estimate the incidence of campylobacteriosis reinfection.[15]

These and other studies have examined reinfection with the same organism within one person. To the best of our knowledge, no study to date has described persons who have experienced multiple episodes of different types of reportable diseases. A study which would consider all reportable diseases could identify subjects with an overall excess of episodes who would otherwise go undetected by public health authorities. It could also characterize these individuals and identify the reportable diseases that they are most likely to acquire. Such an analysis could guide future revisions to public health intervention strategies by identifying potential avenues for the prevention of multiple reportable disease episodes.

The goal of our study was to characterize individuals with multiple reportable disease episodes in Montreal. We aimed to describe the frequency with which persons experience multiple episodes, to describe the individuals who have multiple episodes and to determine the distribution of diseases within these individuals.

METHODS

Study setting

The metropolitan area of Montreal is one of eighteen socio-sanitary regions in the Canadian province of Quebec, which practices ongoing surveillance of communicable diseases. According to the 2006 Canadian census, the Montreal region is home to 1.854 million residents.[16] The diseases for which reporting to the Montreal PHD is mandatory are defined for the entire province of Quebec.[3] They include vaccine-preventable diseases, diseases transmitted by respiratory routes, sexually-transmitted infections (STIs), vector borne diseases, enteric, food and water borne diseases, nosocomial diseases/diseases transmitted by direct contact, and diseases under extreme surveillance.

Data source

As prescribed by provincial law, all reportable diseases diagnosed in Montreal must be reported to the Montreal PHD by doctors and/or laboratory directors. A reportable disease notification received by the Montreal PHD should specify certain personal and non-personal characteristics, such as the disease, the individual's sex, date of birth, and address.[3]

Once a report is received, the data are stored in a database at the Montreal PHD. For this study, we extracted data from this reportable disease database on December 6th, 2013.

Study population

The study population included all Montreal residents with at least one disease episode reported between January 1st, 1990 and December 31st, 2012, inclusive. Reports included both probable and confirmed cases of disease. A subject's first episode was defined as the first one reported to the PHD after January 1st, 1990.

All cases of invasive group B streptococcal disease, enteroviral meningitis, scarlet fever, neonatal herpes, HIV and AIDS reported during the study period were excluded from our analyses as they are no longer considered reportable. Alternatively, conditions that were added to the list of reportable diseases during the study period were included in our analyses, as their inclusion helped to more accurately depict current trends in multiple reportable disease episodes.

A complete list of the 78 reportable diseases included in our study can be found in Appendix 1.

Analysis

An exploratory analysis was performed using descriptive statistics, contingency tables, graphics and logistic regression to describe and compare Montreal residents who experienced one episode (OE) to those who experienced multiple episodes (ME) of reportable diseases.

We began by describing the average number of episodes reported per person between January 1990 and December 2012 and by calculating the median time delay between consecutive episodes using the dates on which the Montreal PHD received a first report. The number of multiple episodes reported per person was stratified by sex in order to observe any differing trends between men and women.

Chi-squared tests were used to determine whether there was a significant difference in the types of diseases reported in subjects with ME and OE and to test whether or not the ten diseases that were more frequently reported in men and women with ME were reported at similar rates in men and women with OE. If significant differences were observed between subjects with ME and OE, a difference of proportions test was then performed within each stratum of reportable disease.

The average number of episodes reported per study subject was calculated in thirty different Montreal neighbourhoods, which were defined as the areas served by local community health centres. A t-test was performed to determine whether or not these values were statistically different from the average number of episodes reported per study subject in all of Montreal.

Finally, in an exploratory attempt to determine whether subjects with ME were less likely than subjects with OE to have been investigated at the time of their first episode, a logistic regression was performed. This logistic regression model also adjusted for all the variables considered in the exploratory analysis: subject's age, sex, neighbourhood, and type of disease acquired at the time of their first episode. The outcome variable, which indicated whether or not the first episode was investigated, was available in 75.9% of cases. A case was defined as having been investigated even if attempts to contact the individual in question were unsuccessful. If this value was missing, a variable which specified the name of the nurse who completed the case investigation served as a proxy. If a name was not provided, we considered the episode to not have been investigated.

All analyses were performed using the R project for statistical computing.[17]

RESULTS

Between January 1st, 1990 and December 31st, 2012, there were 179,455 confirmed or probable episodes reported among 157,839 Montreal residents. Among these 179,455 cases, 50.5% occurred in women, 48.5% occurred in men, and sex was missing in 1.0% of cases. Subjects ranged from 0 to 106 years of age and were on average 30.5 years old, with a median age of 27.0. A peak in disease reports was observed among 0-1 year olds, due to vaccine-preventable diseases and enteric, food and water borne diseases. The number of notifications gradually declined after 1 year of age until a surge of STI cases was observed in 15-19 year olds. The frequency of disease reports was highest in 20-24 year olds, mainly due to STIs. The number of notifications then gradually declined in the older age groups (Figure 1).

Most reported cases were STIs (71.4%), while 19.4% were enteric, food and water borne diseases, 5.7% were diseases preventable by routine vaccination, 2.7% were diseases transmitted by respiratory routes, 0.7% were vector borne and other zoonotic diseases, <0.1% were diseases under extreme surveillance, and <0.1% were nosocomial infections and diseases transmitted through direct contact.

Among the 157,839 subjects included in the study, 15,531 (9.8%) had ME, ranging from two to nineteen episodes. The total number of episodes among individuals with ME accounted for 20.7% of all reported episodes. On average, subjects with OE were 31.1 years of age (median age: 27.0), while subjects with ME were 26.5 years of age (median age: 23.0) at the time of their first episode. The median time delay between two consecutive episodes was 433.0 days (1.2 years), while the minimum delay was 0.0 days (indicating a co-infection) and the maximum was 8,051 days (22.1 years). This maximum time delay was observed in a subject with acute hepatitis B in 1990 and unspecified hepatitis C in 2012.

Among the subjects with ME, 52.9% were women and 47.0% were men. Women accounted for the majority (54.0%) of subjects with four or fewer episodes, while men accounted for the majority (74.3%) of subjects with five or more episodes. The maximum number of episodes reported was ten for women and nineteen for men.

Subjects with ME tended to have more STI reports, while subjects with OE were more likely to acquire diseases preventable by routine vaccination, diseases transmitted by respiratory routes, enteric, food and water borne diseases, as well as vector borne and other zoonotic diseases.

Genital chlamydia and gonorrhea were the two most frequently reported diseases in both men and women with ME (Tables 1 and 2). While infectious syphilis was the third most reported disease in men with ME, it did not figure among the ten most commonly reported diseases in women with ME. In fact, of the 2,696 infectious syphilis cases reported from 1990-2012, 2,578 (95.6%) were reported in men. Despite being among the top ten most reported diseases in both men and women with ME, non-specified hepatitis C and chronic hepatitis B were more commonly reported in individuals with OE (Tables 1 and 2).

The patterns of enteric disease reporting differed between men and women. In women, campylobacteriosis, giardiasis, salmonellosis and shigellosis were all reported at lower rates in subjects with ME. Only amoebiasis was reported statistically more frequently in women with ME, but this result was of borderline significance. Conversely, amoebiasis, giardiasis and shigellosis were all reported at significantly higher rates in men with ME compared to men with OE (Tables 1 and 2).

Of the 152,497 disease reports with a residential address, 15,829 (10.4%) were for subjects residing in the neighbourhood that includes Montreal's gay village. Furthermore, study subjects residing in this neighbourhood had on average 1.16 reports, the highest average number of reports among all neighbourhoods. This neighbourhood was the only one for which its average number of episodes reported per study subject was statistically different from the Montreal average of 1.14 episodes (Appendix 2).

The number of first episodes that were investigated in subjects with OE and ME were 32,746 and 3,666, respectively. These numbers increased to 33,755 (23.7% of all episodes of subjects with OE) and 3,818 (24.6% of all episodes of subjects with ME) when missing values were accounted for. When controlling for age, sex, neighbourhood and type of disease acquired, a multiple logistic regression analysis revealed that subjects with OE were less likely than subjects with ME to have been investigated at the time of their first reportable disease episode [OR: 0.91 (0.87, 0.95)] (Table 3).

DISCUSSION

We described the distribution of multiple reportable disease episodes among Montreal residents from January 1990 to December 2012. More than one episode was reported in 9.8% of subjects and these episodes accounted for 20.7% of all disease reports. Subjects with four to ten episodes were predominantly men, while subjects with eleven to nineteen episodes were exclusively men. STIs were more frequently reported in subjects with ME. Amoebiasis, giardiasis and shigellosis were more commonly reported in men with ME than in men with OE. The highest rate of communicable disease reporting per subject was observed in the neighbourhood that encompasses Montreal's gay village. Finally, our results indicated that

subjects with ME were significantly more likely than subjects with OE to have had their first reportable disease episode investigated.

To the best of our knowledge, this is the first study to consider multiple episodes within individuals across all reportable diseases. The centralized nature of the public health reportable disease database ensured completeness and timeliness of the data. Accordingly, the large number of subjects and the 23 years of data allowed for an exhaustive overview of multiple reportable disease episodes and identification of potential risk factors.

This analysis is the first to quantify the occurrence of several disease reports in a same individual. A remarkable one of every five communicable disease cases reported to the Montreal PHD is diagnosed in a person with more than one disease report. This suggests that focusing intervention efforts on these specific individuals has the potential to translate into a significant decrease in the overall number of communicable disease reports. In fact, the development and adoption of effective public health strategies to manage individuals with many reportable disease episodes can have a large impact in reducing the spread of illness in a population.

While there are many guidelines that propose how to investigate cases of disease in the context of an outbreak, few recommendations have been made concerning how to identify and investigate persons with ME, despite the fact that these individuals place a large burden on public health resources. Identifying these persons as rapidly as possible and providing them with a more personalized intervention may reduce the number of future episodes and prevent further disease transmission. We believe that our results provide a better understanding of who these individuals are and who should be investigated. In particular, our results raise a few noteworthy points.

First, unlike STIs, enteric diseases were reported less frequently in subjects with ME. However, amoebiasis, giardiasis and shigellosis were more common in men with ME than in men with OE. These results support reports in the literature suggesting that certain enteric diseases can be transmitted sexually (a phenomenon described primarily in the men who have sex with men (MSM) community).[18-22] In fact, in Montreal, a 2007 shigellosis outbreak,[23] a 2010-2011 campylobacteriosis outbreak,[24] and a second shigellosis outbreak in 2012-2013,[25] were thought to be the result of sexual transmission among MSM, since contaminated food and water were not found to be at the source of these outbreaks. In Montreal, most cases of enteric disease are investigated only in young children or in the context of an outbreak (with the exception of shigellosis which is always investigated). However, our results suggest that there may be value in also investigating amoebiasis and giardiasis cases reported in adult men. This strategy could help to identify men with potentially riskier sexual practices who would be much harder to identify among the thousands of men reported for an STI each year.

Next, the five neighbourhoods with the highest rates of reporting per study subjects were generally poorer neighbourhoods with high rates of immigration, an indication of the existing reality of health disparities and inequalities.[26-28] According to the 2006 Canadian census, all but one of these neighbourhoods had a median household income which was lower than the median income of all Montreal households,[29-32] and immigrants accounted for 15%-31% of their total population.[33-36] Furthermore, one of these five neighbourhoods encompasses Montreal's gay village, and had the highest average number of reports per subject. This observation is consistent with findings from past studies that have emphasized the high prevalence and incidence of STIs among MSM.[37-40] While there is indeed potential value in directing investigative efforts towards these neighbourhoods, the best way in which to serve these populations remains unclear.

Finally, we found that subjects with ME were more likely than subjects with OE to have been investigated (or, at the very least, to have been attempted to be contacted) at the time of their first reportable disease episode. It is possible that persons with ME are signaled for reportable diseases which are themselves more often targeted by intervention protocols, although this hypothesis is not entirely supported by the output of the logistic regression. Alternatively, this observation may indicate a missed opportunity for prevention and suggests the presence of a core group of individuals with behaviours that are not easily influenced by current public health practices.[13,14] Clearly, preventing recurrent reportable disease episodes is more complex than simply identifying at-risk individuals. An additional and important aspect is the intervention process itself. It is possible that subjects with OE are experiencing better public health interventions than subjects with ME. Consequently, investigation protocols could be tailored according to an individual's history of reportable diseases. For example, unique investigation questionnaires could be issued depending on whether it is a first-, second- or third-time infection. Also, in light of the mounting evidence suggesting the sexual transmission of enteric diseases, the addition of questions in the amoebiasis, giardiasis and shigellosis questionnaires regarding the subject's sexual behaviour may be worthwhile in circumstances where the enteric disease could have been sexually acquired.

This study highlights the importance of analyzing surveillance data from multiple perspectives as the resulting insights can impact on public health strategies. As a result of this analysis, certain changes have already been implemented by the Montreal PHD. Notably, a daily assessment of potential spatial-temporal outbreaks in the city has now been modified to include a stratification of cases by age, sex and residential location. This rather simple adjustment will hopefully result in a more timely detection of an excess of cases and possible outbreaks.

Limitations

This study pertained to residents in the metropolitan area of Montreal and the data collected were contingent on the Montreal PHD's surveillance strategies. The results may therefore not be generalizable to other populations (especially those in rural areas). However, we believe that our results can provide insight and generate discussion in all jurisdictions with a regional public health department receiving reports of incident cases of notifiable diseases.

The true number of persons having had a reportable disease episode and the exact number of episodes they experienced are difficult to estimate for several reasons. First, it is known that cases of reportable diseases are under-reported and that surveillance data provide an under-representation of the real prevalence of disease in a population.[41-43] Also, our analyses did not include any episodes reported prior to 1990, but our long follow-up should minimize any effect of this limitation. We excluded all cases of invasive group B streptococcal disease, enteroviral meningitis, scarlet fever, neonatal herpes, HIV and AIDS. However, it is very unlikely that their exclusion significantly altered our results, since these cases accounted for a small proportion of all reported episodes. Finally, losses to follow-up occurred through the death or relocation of Montreal residents. As a result, not all subjects were followed for the entire study period and their exposure time or time at risk could not be measured precisely. Future studies could link together several regional reportable disease databases in order to reduce censoring bias.

Since the study spanned 23 years, our results are influenced by the many public health achievements and advancements that occurred throughout the study period. The study period also saw modifications made to reportable disease case definitions and investigation guidelines. No inventory of the changes made to investigation protocols during the study period was

available and any changes that occurred may have influenced the results of the logistic regression analysis. Despite these limitations, our results provide a good summary of the overall situation of reportable disease reinfection in the Montreal region from 1990 to 2012.

Future research

While our results offer some insight into how to approach persons with multiple communicable disease episodes, they do not identify specific interventions likely to be of value. Nevertheless, this study does address a large gap in the literature with regards to recurrent episodes of communicable diseases within individuals.

Future studies could identify risk factors associated with having ME and determine the role of factors such as immunosuppression. Additionally, studies which would incorporate indices of social and material deprivation may help in disentangling the mix of structural determinants (poverty, immigration) associated with having ME. Further analyses could also aim to differentiate, for example, subjects with only two reportable disease episodes from those with three or more episodes in order to devise clear policies for investigation and intervention based upon the number of episodes. The results of these and similar analyses could provide clear evidence to support public health officials in their investigative efforts of persons with ME.

Conclusions

Persons with multiple episodes of reportable diseases place a burden not only on public health departments, but also on physicians and health services. The results of this analysis are a first step in developing an evidence-based approach to prioritizing the investigation of disease reports by public health officials. Ultimately, individual behaviours are not changed easily by public health interventions, but at the very least we hope that further research on this topic will

more fully elucidate the risk factors associated with having multiple reportable disease episodes. This evidence may in turn impact the way in which disease reports are prioritized for investigation by public health officials.

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FIGURE 1– Number of communicable diseases (vaccine-preventable diseases, diseases transmitted by respiratory routes, sexually transmitted infections, diseases under extreme surveillance, enteric, food and water borne diseases, nosocomial diseases/diseases transmitted through direct contact, and vector borne diseases) reported by age in Montreal residents from 1990-2012.

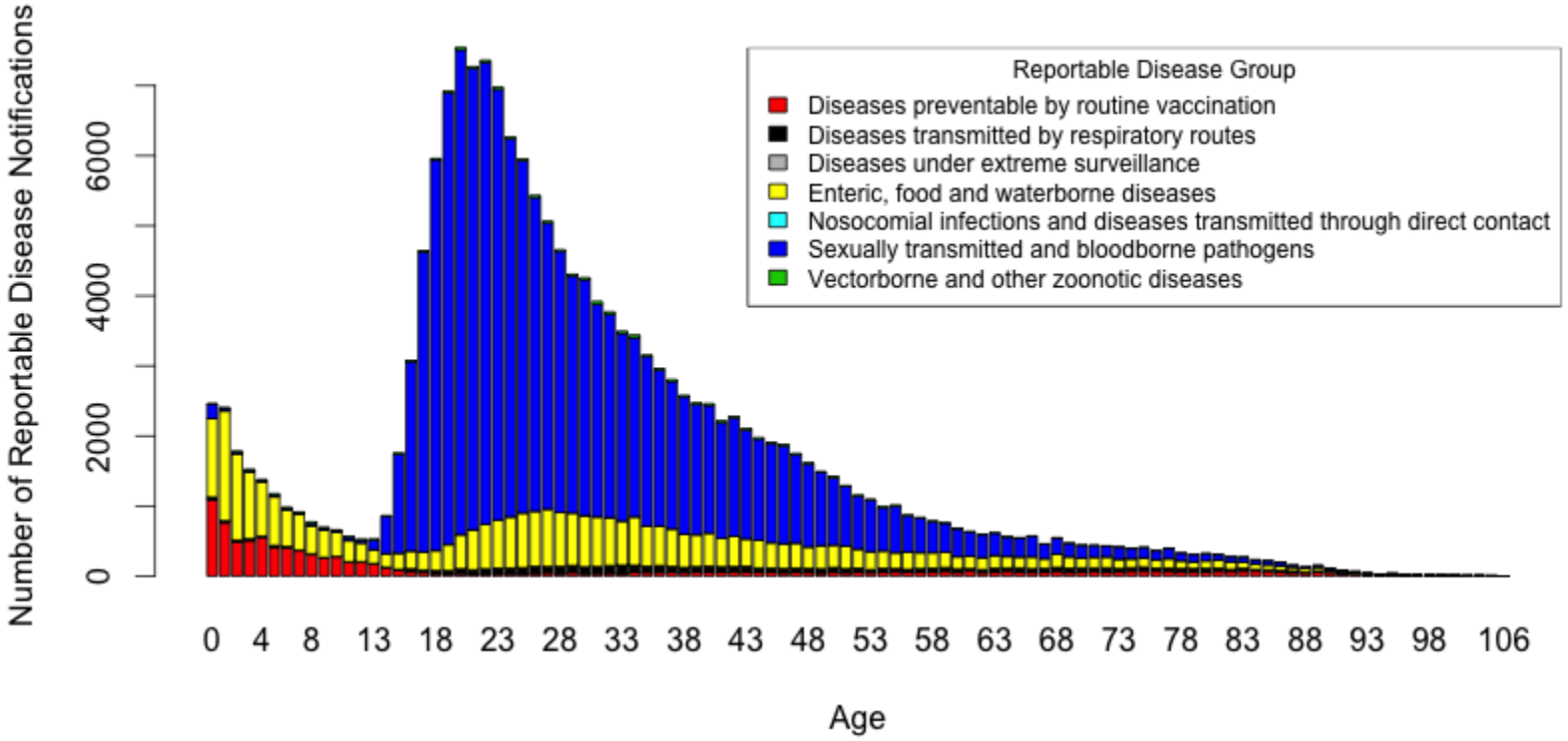


TABLE 1 – Frequency at which the ten most frequently reported communicable diseases in Montreal women with multiple episodes were reported in Montreal women with one episode from 1990-2012.

Note. The 1,736 episodes for which sex was missing were excluded from this analysis, as were the nine episodes which were reported in transsexuals.

[a]A chi-squared test revealed a significant difference between the frequency distributions of the reportable diseases in both women with multiple episodes and in women with one episode ($P<0.01$). Therefore, a test of difference of proportions for each of these ten reportable diseases was subsequently performed.

[b]This refers to the position held in the list of most commonly reported diseases in women with multiple episodes.

[c]This refers to the position held in the list of most commonly reported diseases in women with exactly one episode.

	In women with more than one episode (18,858 episodes reported in total)		In women with exactly one episode (71,733 episodes reported in total)		
	Position[b]	Number of reports (% of total reports)	Position[c]	Number of reports (% of total reports)	Difference of proportions[a] (95% confidence interval)
Genital chlamydia	1	14,021 (74.4)	1	36.669 (51.1)	23.3 (22.5, 24.0)
Gonorrhea	2	1,162 (6.2)	7	2,295 (3.2)	3.0 (2.6, 3.3)
Campylobacteriosis	3	605 (3.2)	4	4,263 (5.9)	-2.7 (-3.0, -2.4)
Non-specified hepatitis C	4	516 (2.7)	3	4,953 (6.9)	-4.2 (-4.5, -3.9)
Giardiasis	5	372 (2.0)	8	1,924 (2.7)	-0.7 (-0.9, -0.5)
Salmonellosis	6	346 (1.8)	5	2,855 (4.0)	-2.2 (-2.4, -1.9)
Chronic Hepatitis B Carrier	7	335 (1.8)	2	5,175 (7.2)	-5.4 (-5.7, -5.2)
Invasive *Streptococcus pneumoniae*	8	181 (1.0)	9	1,662 (2.3)	-1.3 (-1.5, -1.2)
Shigellosis	9	168 (0.9)	12	1,134 (1.6)	-0.7 (-0.9, -0.5)
Amoebiasis	10	162 (0.9)	15	504 (0.7)	0.2 (0.0, 0.3)

TABLE 2 – Frequency at which the ten most frequently reported communicable diseases in Montreal men with multiple episodes were reported in Montreal men with one episode from 1990-2012.

Note. The 1,736 episodes for which sex was missing were excluded from this analysis, as were the nine episodes which were reported in transsexuals.

[a]A chi-squared test revealed a significant difference between the frequency distributions of the reportable diseases in both men with multiple episodes and in men with one episode ($P<0.01$). Therefore, a test of difference of proportions for each of these ten reportable diseases was subsequently performed.

[b]This refers to the position held in the list of most commonly reported diseases in men with multiple episodes.

[c] This refers to the position held in the list of most commonly reported diseases in men with exactly one episode.

	In men with more than one episode (18,247 episodes reported in total)		In men with exactly one episode (68,872 episodes reported in total)		Difference of proportions[a] (95% confidence interval)
	Position[b]	Number of reports (% of total reports)	Position[c]	Number of reports (% of total reports)	
Genital chlamydia	1	5,981 (32.8)	1	16,514 (24.0)	8.8 (8.0, 9.6)
Gonorrhea	2	2,980 (16.3)	3	8,102 (11.8)	4.5 (4.0, 5.2)
Infectious syphilis	3	1,459 (8.0)	14	1,119 (1.6)	6.4 (6.0, 6.8)
Non-specified hepatitis C	4	1,081 (5.9)	2	8,834 (12.8)	-6.9 (-7.3, -6.5)
Amoebiasis	5	958 (5.3)	15	1,111 (1.6)	3.7 (3.3, 4.0)
Giardiasis	6	929 (5.1)	7	2,502 (3.6)	1.5 (1.1, 1.8)
Chronic hepatitis B carrier	7	819 (4.5)	4	6,534 (9.5)	-5.0 (-5.4, -4.6)
Campylobacteriosis	8	754 (4.1)	5	4,862 (7.1)	-3.0 (-3.3, -2.8)
Shigellosis	9	510 (2.8)	11	1,206 (1.8)	1.0 (0.8, 1.3)
Salmonellosis	10	380 (2.1)	6	2,910 (4.2)	-2.1 (-2.4, -1.9)

TABLE 3 – Determinants of a first case investigation in Montreal residents with at least one communicable disease report from 1990-2012.

Note. This table provides the effect measures of the univariate and multiple logistic regression models that were performed to determine the determinants of public health investigation of a subject's first reported communicable disease. The effect measures of each neighbourhood are omitted from the table for simplicity. The cases for which residential location or sex was missing or in which sex was listed as transsexual were excluded from this analysis.

[a]The multiple logistic regression adjusted for a subject's age, sex, and neighbourhood at the time of their first communicable disease episode, as well as the type of disease acquired and a dummy variable specifying whether or not the subject ultimately had multiple episodes from 1990-2012.

Covariate	Univariate logistic regression Odds ratio (95% confidence interval)	Multiple logistic regression[a] Odds ratio (95% confidence interval)
Age (per 10 year increase)	1.09 (1.09, 1.10)	1.04 (1.04, 1.05)
Sex		
Men	1.27 (1.24, 1.30)	1.30 (1.26, 1.33)
Women	1	1
Type of reportable disease		
Diseases preventable by routine vaccination	1	1
Diseases transmitted by respiratory routes	11.51 (1.06, 1.25)	10.20 (9.35, 11.11)
Diseases under extreme surveillance	37.21 (4.80, 288.3)	37.86 (4.87, 294.40)
Enteric, food and water borne diseases	1.32 (1.26, 1.39)	1.23 (1.17, 1.30)
Sexually transmitted and blood borne pathogens	0.86 (0.81, 0.90)	1.04 (0.99, 1.10)
Vector borne and other zoonotic diseases	3.09 (2.74, 3.49)	2.90 (2.56, 3.29)
Nosocomial infections and diseases transmitted through direct contact	4.83e4 (6.97e-27, 3.34e35)	4.47e4 (1.27e-26, 1.58e35)
Multiple communicable disease episodes		
Yes	1	1
No	0.95 (0.92, 0.99)	0.91 (0.87, 0.95)

APPENDIX 1 – List of the communicable diseases for which reporting to the Montreal public health department is mandatory by physicians and/or laboratories.

Diseases preventable by routine vaccination
Congenital Rubella, *Haemophilus influenza*, Invasive *Streptococcus pneumonia*, Measles, Meningococcus, Mumps, Pertussis, Poliomyelitis, Rubella

Diseases transmitted by respiratory routes
Invasive Group A Streptococcal Disease, Legionellosis, Leprosy, Tuberculosis

Diseases under extreme surveillance
Botulism, Cholera, Dengue Fever

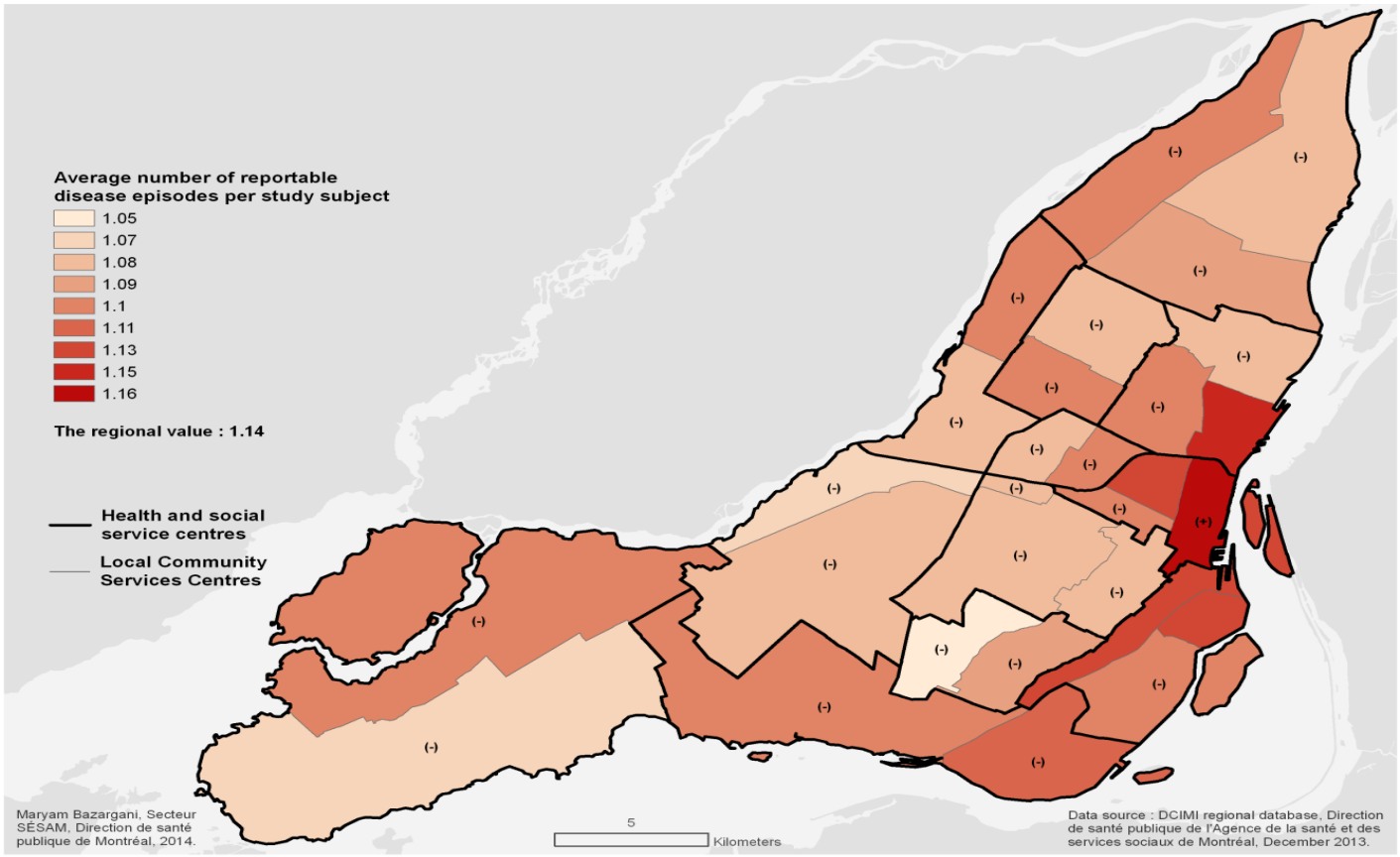
Enteric, food and water borne diseases
Amoebiasis, Brucellosis, Campylobacteriosis, Cryptosporidiosis, Cyclosporiasis, Fish and Shell Toxin Nutritional Infection, Gastro-Enteritis of Unknown Etiology, Giardiasis, Hepatitis A, Hepatitis E, Invasive *Escherichia coli* Infection, Listeriosis, Mushroom Toxin Nutritional Infection, Non-Specified Nutritional Infection, Paratyphoid, Salmonellosis, Shigellosis, *Staphylococcus* Nutritional Infection, Trichinosis, Typhoid, Verotoxigenic *Escherichia coli* Infection, *Vibro parahaemolyticus* Nutritional Infection, *Yersinia enterocolitica*

Nosocomial infections and diseases transmitted through direct contact
Creutzfeldt-Jakob Disease, Vancomycin-Resistant *Staphylococcus aureus* Infection

Sexually transmitted and blood borne pathogens
Acute Hepatitis B, Acute Hepatitis C, Chancroid, Chronic Hepatitis B Carrier, Congenital Syphilis, Genital Chlamydia, Gonorrhea, Hepatitis D, Human T-cell Lymphotropic Virus, Infectious Syphilis, Neurosyphilis, Non-Infectious Syphilis, Non-Specified Hepatitis, Non-Specified Hepatitis B, Non-Specified Hepatitis C, Non-Specified Syphilis, Ocular Chlamydia, Other Forms of Syphilis, Tertiary Syphilis, Pulmonary Chlamydia, Venereal Lymphogranulomatosis

Vector borne and other zoonotic diseases
Babesiosis, Chagas Disease, Leptospirosis, Lyme Disease, Non-Specified Plasmodium Malaria, *Plasmodium falciparum* Malaria, *Plasmodium malariae* Malaria, *Plasmodium ovale* Malaria, *Plasmodium vivax* Malaria, Psittacosis, Q Fever, Rabies, Tularemia, Viral Encephalitis (by arthropods, mosquitos), Viral Encephalitis (by ticks), West Nile Virus

APPENDIX 2 – Average number of communicable disease reports per study subject residing in a Montreal neighbourhood.
Note. The 26,958 cases for which residential location was missing were excluded from this analysis. The (-) symbol is located in neighbourhoods where the average number of reports per subject is significantly lower than the regional value. The (+) symbol is located in neighbourhoods where the average number of reports per subject is significantly greater than the regional value.



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Contributors

M. Caron designed the study, performed the data analyses, interpreted the results, and was the principal writer of this article. L. Bédard and D.L. Buckeridge supervised the study in its entirety, helped design the study and interpret the results, and reviewed the manuscript at all stages. J. Latreille contributed to the interpretation of the results and the review of the article.

Human participant protection

This study received ethics approval from the Institutional Review Board of McGill University's Faculty of Medicine.

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Chapter Four

Predicting Future Sexually Transmitted Infections in Montreal Residents with an Enteric Disease Report

The exploratory analysis discussed in chapter three found that men with multiple episodes were more likely to have cases of amoebiasis, giardiasis and shigellosis reported to public health authorities. Enteric diseases, however, are not generally considered by public health officials to be transmitted through sexual behaviour. As a result, the second part of this thesis focuses more specifically on the sexual transmission of enteric diseases, an occurrence which is common in persons with multiple reportable disease episodes.

This second manuscript outlines the development of a statistical model to predict which individuals with an enteric disease report are at risk of acquiring future sexually transmitted infections. To the best of our knowledge, no model has been built to predict future sexually transmitted infections in persons with an enteric disease report. The manuscript summarizes the validity of this prediction model and describes how its implementation can be beneficial to public health officials.

We intend to submit this manuscript for publication to the Journal of the American Medical Informatics Association and have formatted the manuscript according to this journal's specifications.

Title: Enteric Disease Episodes and the Risk of Acquiring a Future Sexually Transmitted Infection: A Prediction Model in Montreal Residents

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ABSTRACT

Objective. The sexual transmission of enteric diseases poses an important public health challenge. We aimed to build a prediction model capable of identifying individuals with an enteric disease report who could be at risk of acquiring future sexually transmitted infections (STIs).

Materials and Methods. Passive surveillance data on Montreal residents with at least one enteric disease report was used to construct the prediction model. Cases were defined as all subjects with at least one STI report following their initial enteric disease episode. A final logistic regression prediction model was chosen using forward stepwise selection.

Results. The logistic regression prediction model with the greatest validity included the subject's age, sex, residential location, number of STI episodes experienced prior to the first enteric disease episode, type of enteric disease acquired, and an interaction term between age and sex. This model had an area under the curve of 0.77, and had acceptable calibration.

Discussion. A coordinated public health response to the sexual transmission of enteric diseases requires that a distinction be made between cases of enteric diseases transmitted through sexual activity from those transmitted through contaminated food or water. A prediction model can aid public health officials in identifying individuals who may have a higher risk of sexually acquiring a future reportable infection. Once identified, these individuals could receive specialized interventions.

Conclusion. The information produced from a prediction model capable of identifying higher risk individuals can be used to guide efforts to investigate and control reported enteric diseases and STIs.

BACKGROUND AND SIGNIFICANCE

Enteric diseases are usually acquired through ingestion of contaminated food and water. Yet, recent studies have suggested that certain enteric diseases may also be transmitted through sexual activity. This association between enteric diseases and sexual behaviour was first characterized in 1968.[1] Epidemiological studies have subsequently described sexually acquired cases of amoebiasis,[2-8] campylobacteriosis,[9, 10] giardiasis,[8, 11, 12] and shigellosis,[12-16] generally in men who have sex with men (MSM). As a result of this growing phenomenon, drug-resistant enteric disease outbreaks are now frequently observed in large metropolitan areas.[2, 9, 10, 12, 13, 16]

Mounting evidence has suggested that persons with riskier sexual practices are at greater risk of acquiring enteric diseases, presumably via a sexual route. In fact, many studies have suggested that the prevalence of certain enteric diseases is significantly greater in HIV-infected individuals.[3, 4, 8] Furthermore, a retrospective observational study reported that men with multiple episodes of different reportable diseases were significantly more likely than men with one reportable disease episode to be reported for amoebiasis, giardiasis and shigellosis.[17]

Although person-to-person transmission of enteric diseases poses important public health challenges, regional public health departments (PHD) rarely investigate reports of enteric diseases in adults in the absence of a spatial-temporal excess of cases. Furthermore, enteric disease investigation questionnaires generally do not include a sexual behaviour component. Without proper public health interventions in place, individuals who have sexually-acquired an enteric disease remain at risk of acquiring and spreading further sexually transmitted infections (STIs) and the incidence of antibiotic-resistant enteric disease outbreaks is likely to increase.

OBJECTIVES

The objective of our study was to create a prediction model, using passive surveillance data, to identify Montreal residents with an enteric disease report who are at risk of acquiring an STI in the future. While there have been a number of past studies to propose risk models and prediction rules for detecting prevalent cases of STIs in order to encourage selective screening,[18-26] to the best of our knowledge no prediction model has been built to predict future STIs in persons with an enteric disease report. Such a prediction model could allow PHDs to better focus their enteric disease investigative efforts by facilitating the identification of individuals who put themselves and their sexual partners at risk of acquiring future communicable diseases.

MATERIALS AND METHODS

Study setting

The PHD of the metropolitan area of Montreal, in the Canadian province of Quebec, practices ongoing surveillance of reportable diseases, including enteric, food and water borne diseases and infections due to sexually transmitted and blood borne pathogens.

Currently, the Montreal PHD rarely investigates enteric disease reports in the absence of a spatial-temporal excess of cases. Furthermore, only cases of amoebiasis and shigellosis have investigation questionnaires that include questions regarding an individual's sexual behaviour and recent sexual activities.

Data source

As prescribed by provincial law, doctors and laboratory directors must report all cases of notifiable diseases to the Montreal PHD. A reportable disease notification received by the

Montreal PHD should specify the disease, the individual's sex, date of birth, address, and other data.[27] Once a report is received, the data are stored in a database at the Montreal PHD. For this study, we extracted data from this reportable disease database on September 18th, 2013.

Study population

The study population included all Montreal residents with at least one probable or confirmed enteric disease episode reported to the Montreal PHD between January 1st, 1990 and December 31st, 2011, inclusively. All individuals who were less than fourteen years of age at the time of their first enteric disease episode were excluded. The one individual whose sex was listed as transsexual (transitioning from male to female) was also excluded from the study.

Subjects were defined as cases if they had at least one STI report no later than December 31st, 2012, following their initial enteric disease episode. Conversely, controls consisted of all subjects with no STI reports between the time of their first enteric disease episode and December 31st, 2012. Since the average time delay between two consecutive reportable disease episodes in Montreal residents is approximately one year,[17] this ensured that all subjects had a sufficient amount of time to potentially acquire a future STI.

Only the enteric diseases and STIs for which reporting to the Montreal PHD is currently mandatory (Table 1) were included in our analyses.

Table 1 Enteric diseases (classified according to pathogen type) and sexually transmitted infections for which reporting to the Montreal public health department is mandatory by physicians and/or laboratories.[28]

Enteric, Food and Water Borne Diseases		
Bacterial	Parasitic	Unknown/Toxin/Viral
Brucellosis, Campylobacteriosis, Invasive *Escherichia coli* infection, Verotoxigenic *Escherichia coli* infection, Listeriosis, Paratyphoid, Salmonellosis, Shigellosis, *Staphylococcus* nutritional infection, *Vibro parahaemolyticus* nutritional infection, Typhoid, *Yersinia enterocolitica*	Amoebiasis, Cryptosporidiosis, Cyclosporiasis, Giardiasis, Trichinosis	Gastro-enteritis of unknown etiology, Fish and shell toxin nutritional infection, Mushroom toxin nutritional infection, Non-specified nutritional infection, Hepatitis A, Hepatitis E
Sexually Transmitted and Blood Borne Pathogens		
Acute Hepatitis B, Non-Specified Hepatitis B, Chronic Hepatitis B Carrier, Acute Hepatitis C, Non-Specified Hepatitis C, Hepatitis D, Non-Specified Hepatitis, Genital Chlamydia, Ocular Chlamydia, Pulmonary Chlamydia, Infectious Syphilis, Non-Infectious Syphilis, Tertiary Syphilis, Neurosyphilis, Other Forms of Syphilis, Non-Specified Syphilis, Chancroid, Gonorrhea, Human T-cell Lymphotropic Virus, Venereal Lymphogranulomatosis		

Analysis

First, descriptive statistics were calculated to characterize the study population and to assess the baseline characteristics (characteristics at the time of a subject's first enteric disease episode) of both cases and controls.

A logistic regression model was built to predict the probability of a future STI episode. Only data available at the time of the subjects' first enteric disease notification were considered as potential predictors. These data included the age, sex, and neighbourhood of residence (among 29 different local areas of residence) of the subject, the number of STI episodes experienced prior to the first enteric disease episode, the month during which the enteric disease episode was reported, and the type of enteric disease acquired (bacterial, parasitic, or unknown/toxin/viral).

A split-set analysis was performed, such that 70% of subjects were included in the training group and the remaining 30% of subjects were assigned to the testing group.[29] The training group was used to determine the final prediction model, while the testing group assessed the accuracy of the final model.

Univariate logistic regressions were fit prior to building the prediction model. To obtain the final prediction model, a forward stepwise selection technique was applied using the Akaike Information Criterion (AIC). AIC was chosen as a selection criterion as it is widely accepted and offers a good trade-off between model complexity and goodness of fit.[30] Covariates were consecutively added into the prediction model until the addition of a covariate no longer decreased the model's AIC. The order in which the covariates were added to the prediction model depended on the covariates' significance in their respective univariate logistic regression models, such that the most significant covariate was added first, and so on. Added last to the

model was an interaction term between age and sex, in order to account for the possibility that the effect of age varies according to sex.

The final model was applied to the testing data and its discrimination (ie, the extent to which the predicted probabilities distinguished the high risk individuals from the low risk individuals) was assessed using the area under the receiver operating characteristic curve (AUC). The calibration of the model (ie, the extent to which the predicted probabilities agreed with the observed probabilities) was assessed by observing the proportion of true cases in each decile of predicted probability.

Sensitivity analyses

Since time-to-event information was available, a survival analysis was performed in order to assess whether this would improve the performance of the prediction model. Using only the predictors included in the final logistic regression prediction model, we constructed a Cox proportional hazards prediction model. The same study population (including the same training and testing groups) was used to construct and to validate the Cox model. The effect measures were calculated using the training population only, while the testing population was used to calculate the Cox model's AUC. The AUC and the effect measures from the Cox prediction model were compared to those of the logistic regression prediction model in order to determine if the predictive powers of these two models were comparable.

All analyses were performed using the R project for statistical computing.[31]

RESULTS

Our study population included 22,156 Montreal residents with at least one confirmed or probable enteric disease episode reported to the Montreal PHD between January 1st, 1990 and

December 31st, 2011, inclusively. The 986 individuals with an STI report after their initial enteric disease episode were defined as cases, while the remaining 21,170 individuals were listed as controls.

Baseline characteristics (characteristics at the time of a subject's first enteric disease episode) were assessed for both cases and controls (Table 2).

Table 2 Characteristics of Montreal residents older than 14 years of age at the time of their first enteric disease episode (at baseline).

Baseline characteristics		Cases (n = 986)	Controls (n = 21,170)
Age			
	Minimum	14	14
	Median	32.0	35.0
	Mean	33.2	40.2
	Maximum	93	106
		SD=11.3	SD=18.1
Gender (%)			
	Women	193 (19.6)	9,405 (44.4)
	Men	793 (80.4)	11,693 (55.2)
	Missing	0 (0.0)	72 (0.3)
Number of prior STIs			
	Minimum	0	0
	Median	0.0	0.0
	Mean	0.3	0.0
	Maximum	11	7
		SD=0.9	SD=0.2
Month (%)			
	January	83 (8.4)	1,474 (7.0)
	February	72 (7.3)	1,452 (6.9)
	March	76 (7.7)	1,552 (7.3)
	April	62 (6.3)	1,480 (7.0)
	May	86 (8.7)	1,727 (8.2)
	June	80 (8.1)	1,726 (8.2)
	July	88 (8.9)	2,084 (9.8)
	August	101 (10.2)	2,375 (11.2)
	September	113 (11.5)	2,256 (10.7)
	October	81 (8.2)	1,960 (9.3)
	November	77 (7.8)	1,642 (7.8)
	December	67 (6.8)	1,442 (6.8)
Type of enteric disease (%)			
	Bacterial	412 (41.8)	13,979 (66.0)
	Parasitic	361 (36.6)	4,924 (23.3)
	Toxin/Unknown/Viral	213 (21.6)	2,267 (10.7)

Men comprised the majority of cases (80.4%), but accounted for a smaller percentage of controls (55.2%). On average, cases acquired their first enteric disease at 33.2 years of age, while controls were slightly older (40.2 years of age). The median number of prior STI episodes experienced was 0 in both cases and controls; however the maximum number of prior STI reports was 11 in cases and 7 in controls. The months with the greatest number of first enteric disease reports were August and September for both cases and controls. First enteric disease episodes were primarily of parasitic or viral/toxin/unknown etiology in cases (58.2%), while bacterial infections were principally reported in controls (66.0%).

Age, sex, residential location, number of prior STIs experienced and type of enteric disease acquired were all significant predictors in their respective univariate logistic regression models (Table 3).

Table 3 Logistic regression effect measures for acquiring a future sexually transmitted infection among Montreal residents with at least one enteric disease episode from 1990-2012. The effect measures of each neighbourhood are omitted from the table for simplicity.

	Univariate logistic regression		Multiple logistic regression (Final prediction model)	
	Unadjusted odds ratio	95% CI	Adjusted odds ratio	95% CI
Age (per 10 year increase)	0.76	(0.72, 0.81)	0.48	(0.39, 0.58)
Sex				
Men	3.39	(2.79, 4.12)	0.42	(0.22, 0.80)
Women	1	-	1	-
Age*Sex	-	-	1.06	(1.04,1.08)
Number of prior STIs	4.59	(3.84, 5.49)	3.86	(3.19, 4.67)
Month of enteric disease report				
January	1.43	(0.99, 2.08)		
February	1.19	(0.80, 1.76)		
March	1.13	(0.76, 1.66)		
April	0.91	(0.60, 1.38)		
May	0.96	(0.65, 1.42)		
June	1.13	(0.78, 1.64)		
July	1.06	(0.73, 1.52)	-	-
August	1.02	(0.72, 1.46)		
September	1.13	(0.79, 1.61)		
October	1.10	(0.75, 1.62)		
November	1.16	(0.78, 1.72)		
December	1	-		
Type of enteric disease				
Bacterial	0.39	(0.32, 0.46)	0.56	(0.46, 0.68)
Parasitic	1	-	1	-
Toxin/Unknown/Viral	1.28	(1.04, 1.59)	1.38	(1.10, 1.74)

As a result, during the forward stepwise selection, these variables were added to the prediction model first. Despite not being significant in the univariate analysis, the variable specifying the month during which the enteric disease episode was reported to the PHD was added to the prediction model last to confirm that the prediction model did not improve due to its inclusion.

The final prediction model (the model with the lowest AIC) included as predictors the subject's age, sex, residential location, number of STI episodes experienced prior to the first enteric disease episode, as well as the type of enteric disease acquired, and an interaction term between age and sex (Table 3). When validated on the testing subjects, the prediction model had an AUC of 0.77 (Figure 1). Its calibration can be assessed in Figure 2.

The predictors included in this logistic regression prediction model were incorporated in a Cox proportional hazards prediction model as part of a sensitivity analysis. This Cox prediction model had an AUC of 0.76 and similar effect measures to those of the logistic regression prediction model (results presented in supplementary material).

DISCUSSION

We developed and evaluated a model for predicting the risk of acquiring a future STI among Montreal residents with an enteric disease report. The covariates included in the final logistic regression prediction model were subject's age, sex, residential location, and number of STI episodes experienced prior to the first enteric disease episode, as well as the type of enteric disease acquired, and an interaction term between age and sex (Table 3). This model had an AUC of 0.77 (Figure 1) and appeared to have relatively good agreement between the predicted and observed outcomes overall (Figure 2). A Cox proportional hazards model, built using the

same final predictors, had a similar predictive power with an AUC of 0.76 and effect measures similar to those of the logistic regression (supplementary material).

To the best of our knowledge, this study is the first of its kind to attempt to build a prediction model capable of assessing the risk of acquiring a future STI in individuals with an enteric disease report. Our prediction models, which were constructed using a large number of subjects and 23 years' worth of surveillance data can be used to inform the way in which PHDs investigate incident cases of enteric diseases.

A coordinated public health response to the observed increase in sexual transmission of enteric diseases will require that a distinction be made between cases of enteric diseases transmitted through sexual activity from those transmitted through contaminated food or water. While our prediction models do not predict whether or not an enteric disease was sexually acquired, they do provide a first step in identifying individuals at risk of sexually acquiring further infections based on their age, sex, residential location, history of prior STIs, and type of enteric disease acquired.

Our models suggest that persons with an enteric disease report who are at greater risk of acquiring a future STI are younger men with a history of STIs. These individuals are also more likely to have an enteric disease classified as either parasitic or of viral/toxin/unknown etiology, rather than bacterial in nature. Furthermore, while not presented in our tables, greater odds of the outcome were observed in the neighbourhood encompassing Montreal's gay village. This result is not surprising, since enteric disease outbreaks due to sexual transmission were observed primarily in MSM.[3, 5, 7, 9, 10, 13, 14, 16] Furthermore, this is consistent with observations that STIs are more frequent in the MSM community.[32-35] Despite not having a MSM variable

available in our dataset, the neighbourhood variable likely captured some of its predictive effect. Additionally, increased odds of the outcome were observed in low-income neighbourhoods with high rates of immigration indicating that these may be strong predictors for acquiring a future STI. This is consistent with previous risk model studies, which suggest that a person's area of residence,[20, 36] and ethnicity,[20-22, 24, 36] are STI risk factors.

Given these results, public health officials could attempt to identify enteric disease cases that may have been sexually acquired based on the presence of the aforementioned risk factors. However, this approach is ambiguous and imprecise. On the other hand, the implementation of a prediction model, such as the ones described in this article, provides a more quantifiable and objective approach to identifying cases of enteric diseases that may have been sexually acquired.

In practice, the implementation by public health authorities of a logistic regression prediction model would likely be more intuitive and straight-forward than the implementation of a Cox model, since a logistic regression can more readily assign probabilities of acquiring the outcome to every individual. Furthermore, our results show that the logistic regression model performs just as well as the Cox model, since the additional time-to-event information included in the Cox prediction model did not appear to increase its validity. Using a logistic regression prediction model would simply require that public health officials investigate persons with an assigned probability above a certain threshold, which would be selected according to the desired sensitivity and specificity of the prediction model.

Our logistic regression prediction model had high accuracy and acceptable calibration. Seeing as the outcome is rare, our prediction model assigned a high probability of developing the outcome to very few subjects. As a result of this rare outcome, our prediction model works best

when a lower probability threshold is chosen. In fact, the threshold at the optimal operating point of the AUC (the point at which the Euclidean distance is smallest) is 0.041, which is similar to the event rate in our study population (~ 4.5%). Using a threshold of 4.1%, our prediction model has a sensitivity and specificity of 0.73 and 0.67, respectively, and positive and negative predictive values of 0.10 and 0.98, respectively. This can be better appreciated quantitatively: Among the 6,313 subjects included in the testing group who were assigned a probability by the prediction model, 295 were cases and 6,018 were controls. When using the optimal threshold of 4.1%, 2,179 subjects were flagged by the prediction model as being at risk of acquiring an STI in the future, of which 216 were true positives and 1,963 were false positives.

A prediction model capable of identifying individuals at high-risk of an STI following an enteric disease episode is a practical tool that can support efforts to prevent the acquisition of STIs and perhaps sexually acquired enteric diseases. Once identified, these individuals could receive appropriate and specialized interventions. For example, in addition to asking individuals with enteric diseases about their eating habits and past travels, individuals flagged by the model, could also be asked about their sexual practices. If the answers to these questions suggest that the individual likely acquired the enteric disease through sexual practices, STI testing can be recommended to them as well as to their partners.

The use of a prediction model to identify high-risk individuals who require a more personalized intervention is one way in which public health authorities can use evidence to prioritize the investigation of reportable diseases and potentially reduce the number of outbreaks due to the sexual transmission of enteric pathogens. Other public health strategies include educating the public on the possibility of acquiring enteric diseases through sexual activity. In January 2014, Public Health England launched an awareness campaign aiming to educate its gay

and bisexual population on the risks of sexually acquiring and transmitting shigellosis.[37] While this campaign is the first of its kind to raise awareness about the sexual transmission of enteric diseases, more are likely to follow as the number of drug-resistant enteric disease outbreaks continues to rise.

Limitations

The prediction model was constructed using surveillance data from the Montreal metropolitan area. Consequently, the model is specific to Montreal residents. Nevertheless, the modeling approach used and the results are likely generalizable to other large North American cities, but may not apply to rural populations.

The use of passive data likely resulted in an under-representation of the true number of enteric disease and STI episodes experienced in Montreal residents. It is estimated that less than 10% of enteric disease episodes are reported to public health authorities.[38] However, since our prediction model was built using 23 years of data, we believe that the subjects included in our study were unlikely to be biased or unrepresentative of the true population. On the other hand, since the study spanned a 23 year period, our prediction model may have been affected by societal changes, as well as advances in public health intervention strategies, but it is unlikely that calendar time had a significant effect on our results.

Our study population was not a closed cohort, and no data were available with regards to subject death or relocation outside of Montreal. We therefore assumed that all individuals were followed until the end of the study period. However, given the large number of subjects included in the study, it is doubtful that this assumption had a considerable effect on the prediction model's results.

Finally, since the mode of transmission of each enteric disease report was unavailable, we could not directly evaluate the risk factors associated with sexually acquiring an enteric disease episode.

Future research

External validation of this prediction model remains to be performed. Additionally, future studies should evaluate its effectiveness in practice and recommend modifications that may improve its performance in practical settings and reduce its number of false positives. Such modifications could consist of the addition in the model of further risk factors (which were unavailable in our dataset), such as psycho-socio-behavioural characteristics.

Finally, epidemiological studies could be performed on cohorts with a confirmed mode of enteric disease transmission, so that potential risk factors for the sexual transmission of enteric diseases can be determined and a further understanding of this topic can be provided.

CONCLUSION

Regional public health departments monitor enteric disease reports in order to ensure the timely detection of a spatial-temporal excess of cases in the event of a contaminated food or water supply. Until recently, the possibility that these diseases may have been sexually acquired was rarely considered. Given the recent increase in sexual transmission of enteric diseases, investigation of presumed cases of sexually acquired enteric diseases can reduce the risks of reinfection and further disease transmission. A prediction model can aid public health officials in identifying individuals who may have a higher risk of sexually acquiring a future infection.

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Contributors MC, LB, DLB, and RB designed the study. MC performed the data analyses. MC, LB, DLB, RB and JL interpreted the results. MC wrote the paper and incorporated revisions. LB and DLB reviewed the manuscript at all stages.

Ethics Approval Institutional Review Board of McGill University's Faculty of Medicine.

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Figure 1 Receiver operating curve of the final logistic regression prediction model. The final logistic regression prediction model included the subject's age, sex, residential location, number of STI episodes experienced prior to the first enteric disease episode, as well as the type of enteric disease acquired, and an interaction term between age and sex. The area under the model's receiver operating curve was 0.77.

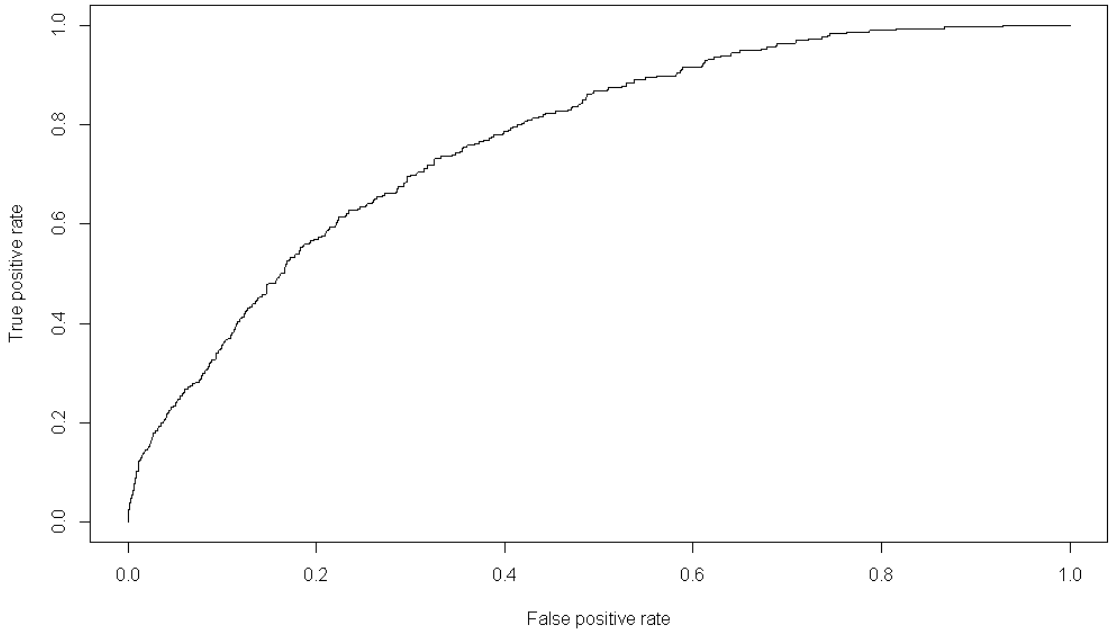
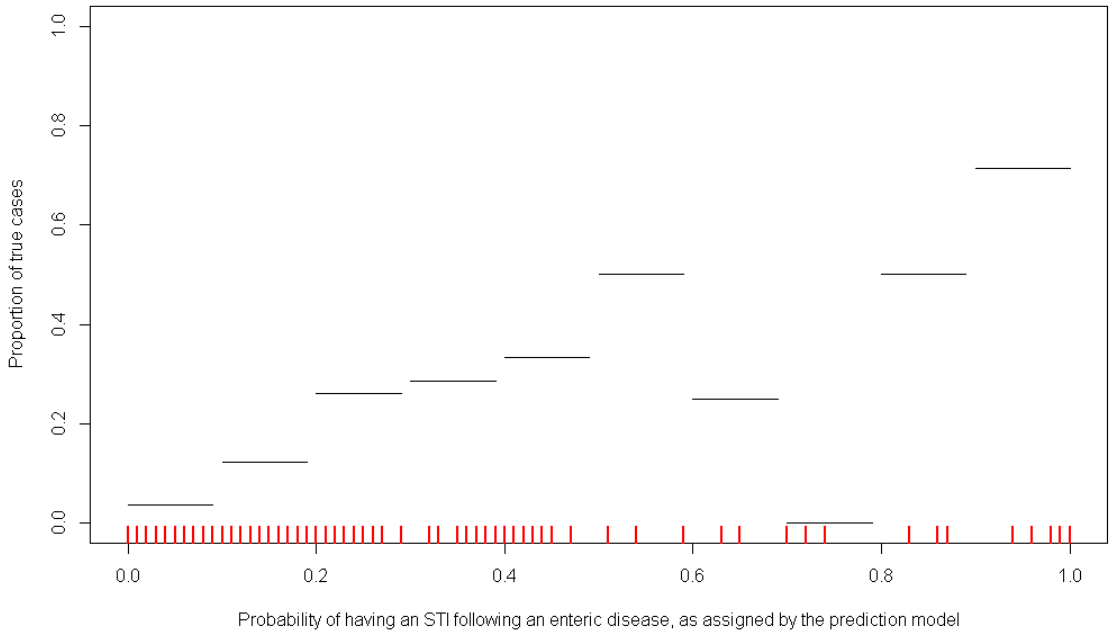


Figure 2 Calibration of the final logistic regression prediction model. The proportion of true cases among each decile of predicted probability is shown. A "rug" is visible on the bottom of the graph depicting all of the probability values that were assigned by the prediction model.



Supplementary Material Cox effect measures for acquiring a future sexually transmitted infection among Montreal residents with at least one enteric disease episode from 1990-2012. The effect measures of each neighbourhood are omitted from the table for simplicity.

	Univariate cox model		Multiple cox model	
	Unadjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Age (per 10 year increase)	0.78	(0.74, 0.83)	0.48	(0.39, 0.58)
Sex				
Men	3.25	(2.69, 3.94)	0.36	(0.20, 0.67)
Women	1	-	1	-
Age*Sex	-	-	1.06	(1.04,1.09)
Number of prior STIs	1.84	(1.75, 1.93)	1.88	(1.78, 2.00)
Month of enteric disease report				
January	1.36	(0.94, 1.95)		
February	1.13	(0.77, 1.66)		
March	1.08	(0.74, 1.58)		
April	0.89	(0.59, 1.33)		
May	0.92	(0.63, 1.35)		
June	1.09	(0.75, 1.57)		
July	1.04	(0.72, 1.48)	-	-
August	1.00	(0.70, 1.42)		
September	1.12	(0.79, 1.59)		
October	1.10	(0.75, 1.60)		
November	1.15	(0.78, 1.68)		
December	1	-		
Type of enteric disease				
Bacterial	0.39	(0.33, 0.46)	0.52	(0.43, 0.62)
Parasitic	1	-	1	-
Toxin/Unknown/Viral	1.10	(0.90, 1.35)	1.02	(0.82, 1.26)

Chapter Five

Conclusion

Communicable disease surveillance, achieved primarily through mandatory reporting of infectious diseases to public health officials, protects the health of the population and prevents the spread of disease. These outcomes are achieved in part through thorough case investigations in both the presence and absence of a disease outbreak. When deciding which cases to investigate, local PHDs tend to follow their own guidelines, based on the intervention priorities identified in their region. Despite these measures, no protocols exist to deal with people who have multiple episodes of reportable diseases, even though they place a large burden on health services.

This thesis provided an overview of multiple communicable disease episodes in Montreal residents. It showed that persons with multiple episodes of reportable diseases account for approximately 20% of communicable disease notifications received by public health officials. Furthermore, it revealed that certain episodes of enteric diseases, such as amoebiasis, giardiasis and shigellosis, were more frequently reported in men with multiple communicable disease episodes. This adds to the mounting evidence suggesting that certain populations may be at risk of acquiring enteric diseases through sexual transmission.

In order to help public health authorities respond to the growing number of sexually acquired enteric disease cases, which are often observed in persons with multiple

reportable disease episodes, the second part of this thesis focused on developing and evaluating a model for predicting the risk of acquiring a future STI among Montreal residents with an enteric disease report. The best prediction model was a logistic regression that accounted for a person's age, sex, residential location, history of STIs and type of enteric disease.

This thesis is the first epidemiological study to describe and analyze multiple communicable disease episodes, while accounting for all reportable diseases. The results of the exploratory analysis offer an extensive overview of the situation, and describe the differences in disease reporting between individuals with one and more than one communicable disease episode. The prediction model developed in the second part of this thesis is a novel tool that will be of interest to public health authorities, as it is a quantitative tool to identify individuals with an enteric disease report who are at risk of acquiring future STIs.

The results of these analyses are a first step in developing evidence-based approaches to prioritizing the investigation of disease reports. In fact, certain recommendations should be considered in light of these results. For example, PHDs could consider modifying investigation protocols by creating questionnaires tailored to subjects with multiple reportable disease episodes, and by adding a sexual behaviour component to questionnaires for amoebiasis, giardiasis and shigellosis (if not already the case). Furthermore, adopting a prediction model could help identify potential high-risk individuals who may be worth investigating. The implementation of a valid logistic regression prediction model, such as the one developed in this thesis, would be intuitive

and straight-forward and could guide efforts to investigate and control reported infectious diseases.

Further research is necessary to better identify risk factors associated with having multiple reportable disease episodes. Furthermore, future studies should focus on identifying specific interventions that will support public health officials in their investigative efforts of persons with recurrent episodes of communicable diseases. This includes evaluating the effectiveness of prediction models in practice and recommending modifications that may improve their performance in practical settings.

While the exact way of handling persons who have multiple communicable disease episodes remain to be assessed, it is indisputable that future modifications made to investigation protocols and guidelines must account for the fact that an excess number of cases can not only be within a time and place, but also within an individual. The development of proper guidelines to effectively intervene on persons with multiple communicable disease reports can have a significant impact, as persons with multiple episodes account for a substantial proportion of reportable disease notifications. Simply focusing investigative efforts on these individuals has the potential to translate into a significant decrease in the overall number of communicable disease reports. Consequently, changes made to investigation questionnaires and the implementation of a valid prediction model may be effective public health strategies to manage individuals with many reportable disease episodes and may have an impact in reducing the spread of illness in a population.

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