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ACUTE HEPATITIS IN CHILDREN IN CANADA

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CANADA COMMUNICABLE DISEASE REPORT

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ccdr-rmtc@phac-aspc.gc.ca
613.301.9930

Photo credit
The cover photo represents acute severe hepatitis in children, a rare condition in Canada. The image was taken from Adobe Stock #510539982.

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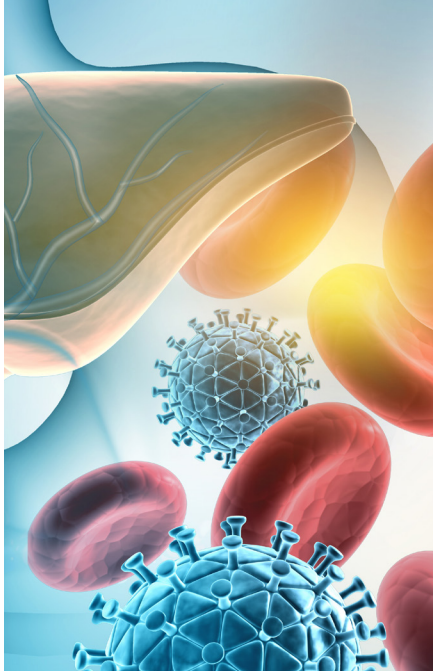**CANADA COMMUNICABLE DISEASE REPORT**

ACUTE HEPATITIS IN CHILDREN IN CANADA

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Investigation of acute severe hepatitis in children: A review of liver transplant data, Canada, 2021–2022

Vanessa Morton[1]*, Meghan Hamel[2], Vicky Ng[3], Susan Gilmour[4], Fernando Alvarez[5], Marina I Salvadori[6,7]

Abstract

An increase in severe acute hepatitis of unknown etiology was first reported in the United Kingdom in April 2022. Following this report, the Public Health Agency of Canada connected with three paediatric liver transplant centres across Canada to determine if an increase in liver transplants was noted. Data demonstrated no observable increase in the number of transplants conducted in 2022. These data in conjunction with a federal, provincial, territorial investigation provided insight into the situation in Canada.

Affiliations

[1] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Guelph, ON

[2] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

[3] SickKids Transplant Center, The Hospital for Sick Children, Toronto, ON

[4] Pediatrics, Stollery Children's Hospital, Edmonton, AB

[5] Division of Paediatric Gastroenterology, Hospital Sainte-Justine, Montréal, QC

[6] Public Health Agency of Canada, Ottawa, ON

[7] Department of Pediatrics, McGill University, Montréal, QC

*Correspondence:
vanessa.morton@phac-aspc.gc.ca

Introduction

In April 2022, the World Health Organization was notified of 10 cases of severe acute hepatitis of unknown etiology in children in the United Kingdom (1). Since this information became known, additional cases of acute hepatitis have been reported in multiple countries worldwide. As of July 8, 2022, 35 countries have reported 1,010 probable cases of severe acute hepatitis of unknown etiology in children since October 2021 (2). In Canada, acute hepatitis is not a reportable disease therefore, there were no surveillance data available to determine if Canada was experiencing any unusual increases in the number of children presenting with acute hepatitis. Acute hepatitis in children does occur, and frequently the etiology is unknown. It occurs along a spectrum from asymptomatic elevation of liver enzymes to liver failure (3). Even without a specific diagnosis, most children recover fully with supportive care. The rarest outcome is fulminant liver failure that necessitates liver transplantation. One approach to determine if there is an increase in acute fulminant hepatitis in children is to collect data on yearly numbers of paediatric liver transplants. This report provides a summary of an investigation of paediatric liver transplantation in Canada.
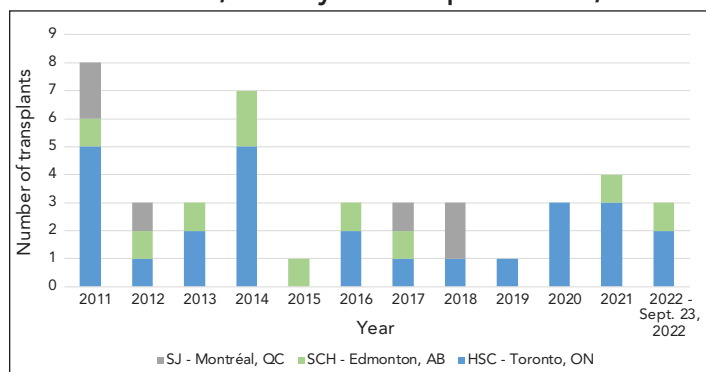
Investigation

All paediatric liver transplants in Canada are performed at one of three transplant centres: Stollery Children's Hospital (SCH, Edmonton, Alberta), The Hospital for Sick Children (HSC, Toronto, Ontario) and "Le Centre hospitalier universitaire Sainte-Justine" (SJ, Montréal, Québec). Data pertaining to the number of liver transplants occurring in children under 16 years of age for paediatric acute liver failure was collected from all three centres. This investigation included cases of acute hepatitis, not attributable to viruses A–E, leading to liver transplant; including those diagnosed with autoimmune hepatitis. Cases with metabolic, genetic, congenital, oncologic, vascular or ischemia conditions or known toxin etiologies that would lead to hepatitis were excluded.

A total of 39 paediatric liver transplants occurred in Canada between 2011 and 2021, with a mean of 3.5 (median: 3; range: 1–8) each year (**Figure 1**). The majority (61.5%) of liver transplants occurred at one institution (HSC). As of August 2022, three liver transplants have been done in 2022.

Figure 1: Number of liver transplants in children under 16 years of age due to acute liver failure by transplant centre in Canada, January 2011–September 23, 2022

Abbreviations: AB, Alberta; HSC, Hospital for Sick Children; ON, Ontario; QC, Québec; SCH, Stollery Children's Hospital; SJ, Le Centre hospitalier universitaire Sainte-Justine

The national investigation of acute hepatitis of unknown origin focused on cases occurring since October 2021 (4). When the investigation was closed on September 23, 2022, a total of four cases of acute hepatitis that resulted in a liver transplant were identified in Canada, one in 2021 and three in 2022.

Discussion

Based on the available data there was no apparent increase in the number of paediatric liver transplants during the period of interest from October 2021 to September 23, 2022, in Canada. This supported the findings of another Canadian investigation, which did not identify any increase in acute hepatitis of unknown etiology in children (4). A federal/provincial/territorial investigation was conducted to actively look for cases of acute hepatitis of unknown origin in children and found no increase in the number of cases of severe acute hepatitis in children.

Since there are only three paediatric transplant centres in Canada, each with specialists who have established working relationships, the Public Health Agency of Canada was able to connect quickly with specialists and determine if they were experiencing an increased need for paediatric liver transplants. This provided a quick mechanism to determine if there were any concerning trends observed in paediatric liver transplants in Canada. Collecting historical baseline data from the transplant centres provided further evidence to support the findings that there had been no increase in paediatric liver transplantation.

There are many causes of paediatric acute liver failure, including infectious agents, metabolic diseases and toxigenic causes; however, in up to 50% of cases, the cause is unknown (3). At the preliminary stage of the investigation, it was important to have a broad case definition to ensure that all possible cases were included. Cases with other known hepatotropic viruses (e.g. human herpes virus, Epstein-Barr virus) were also included because of the possibility of co-infection with an unknown or new viral strain. Similarly, cases with autoimmune hepatitis were included because of the possibility that the condition was triggered or exacerbated by a viral infection.

Since initially reporting on an increase in acute hepatitis in children, the investigation in the United Kingdom has developed a hypothesis that cases of acute hepatitis were triggered by co-infection with adenovirus, or human herpesvirus 6B, and adenovirus-associated virus (AAV2) (5,6). Investigation in the United States also found cases of co-infection with AAV2 and adenovirus (7). Additional research is needed to understand the role of co-infection in the development of acute hepatitis in children.

Limitations
This study is limited to reporting on trends in the number of paediatric liver transplants in Canada. Detailed medical records of cases were not examined; therefore, the causes of liver transplantation were not analyzed for any trends or commonalities.

Conclusion
No observable increase in the number of paediatric transplants conducted from October 2021 to September 23, 2022, was seen in the three Canadian transplant centres. Additional research is needed to understand the role of co-infection in the development of paediatric acute hepatitis.

Authors' statement

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Acute severe hepatitis of unknown origin in children in Canada

Jennifer Macri[1], Vanessa Morton[2], Meghan Hamel[3]*, Pierre-Luc Trépanier[4], Marina I Salvadori[5,6], Acute Hepatitis Investigation Team

Abstract

Background: In spring 2022, a series of reports from the United Kingdom and the United States identified an increase in the incidence of acute severe hepatitis in children. The Public Health Agency of Canada (PHAC) collaborated with provincial/territorial health partners to investigate in Canada. Clinical hepatitis, or inflammation of the liver, is not reportable in Canada, so to determine if an increase was occurring above historical levels, the baseline incidence in Canada was estimated. This article estimates the pre-existing baseline incidence of acute severe hepatitis of unknown origin in children in Canada using administrative databases. It further summarizes the outbreak investigation using information from the national case report forms.

Methods: A committee with representatives from PHAC and provincial/territorial health partners was established to investigate current cases in Canada. A national probable case definition and case report form were developed, and intentionally created to be highly sensitive to capture all potential cases for etiological investigations. To estimate a nationally representative baseline incidence, hospitalization data were extracted from the Discharge Abstract Database and was combined with data from Québec from the *Ministère de la Santé et des Services sociaux*.

Results: Twenty-eight probable cases of acute severe hepatitis of unknown origin in children were reported between October 1, 2021, to September 23, 2022, by six provinces: British Columbia=1; Alberta=5; Saskatchewan=1; Manitoba=3; Ontario=14; and Québec=4. The estimated national baseline incidence was an average of 70 cases annually, or 5.8 cases per month.

Conclusion: There was no apparent increase above the estimated historical baseline levels.

Affiliations

[1] Canadian Field Epidemiology Program, Public Health Agency of Canada, Ottawa, ON

[2] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Guelph, ON

[3] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

[4] Ministère de la Santé et des Services sociaux, Montréal, QC

[5] Public Health Agency of Canada, Ottawa, ON

[6] Department of Paediatrics, McGill University, Montréal, QC

*Correspondence:

meghan.hamel@phac-aspc.gc.ca

Introduction

On April 5, 2022, the World Health Organization (WHO) was notified of a reported increase in the number of cases of acute severe hepatitis in children in the United Kingdom (UK). These cases of hepatitis were not caused by any known hepatitis virus or other typical causes of hepatitis (1). The Public Health Agency of Canada (PHAC) collaborated with provincial/territorial health partners to investigate cases in Canada. Globally, a total of 1,010 probable cases which met the WHO probable case definition have been reported from 35 countries as of July 8, 2022 (1).

Hepatitis is an inflammation of the liver (2) and can be caused by infectious (usually viral) or non-infectious agents (e.g. alcohol, certain drugs) (3). Acute hepatitis ranges widely in severity, from mild to severe, and rarely progresses to liver failure (3). Depending on the cause of hepatitis, the progression to liver failure can be acute and rapid, over a few days to weeks, or can occur very slowly (2). Acute severe hepatitis in children is a rare condition and the etiology is often unknown (2).

Following the initial reports of an increase in cases of acute severe hepatitis of unknown origin, many potential causative agents or associations were hypothesized. Infection with adenovirus 41 was hypothesized due to the detection of the virus in a high proportion of cases in multiple countries: 65% in the UK (4) and 45% in the United States (5). Adenovirus 41 had not previously been associated with hepatitis in immunocompetent children, which the majority of the cases of acute severe hepatitis were. Additional or abnormal susceptibility, co-infections, environmental exposures or a novel adenovirus variant were also investigated as causative agents (1,5). Recent studies have hypothesized association with adeno-associated virus 2 (AAV-2), after identifying this co-infection in cases infected with adenovirus 41 (5,6). Adeno-associated virus 2 has not previously been known to be associated with hepatitis (5–7) Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was also hypothesized as a cause of this condition due to the ongoing coronavirus disease 2019 (COVID-19) pandemic (4). There was no evidence of an association between any SARS-CoV-2 vaccine and acute severe hepatitis in children (8).

In Canada, there is no ongoing surveillance for hepatitis cases that are not caused by a hepatitis virus at the national level. Therefore, an estimation of the baseline incidence of acute severe hepatitis of unknown origin in children was needed to ascertain whether an increase in cases was being observed in Canada. The objective of this work was to estimate the baseline number of cases in Canada before 2021 and to investigate the incident cases of acute severe hepatitis of unknown origin in children in Canada as of October 2021.

Methods

An investigation committee led by PHAC with representatives from each province and territory was established on April 29, 2022. Provinces and territories began active prospective monitoring for cases and conducted a retrospective review up to October 1, 2021 (six months prior to the initial notification of increase of cases by the WHO) to identify any probable cases that met the established case definition. Temporary mandatory reporting or ministry directives were established in each jurisdiction to facilitate national reporting of probable cases. Retrospective chart reviews were conducted by the provinces/territories to identify cases which had occurred between October 1, 2021, but prior to the start of the investigation in April 2022. Any probable cases which met the criteria outlined in the national case definition were included in the national investigation. Surveillance for the purposes of the national investigation was completed on September 23, 2022.

As this condition was not under surveillance prior to this investigation, an estimate of a national baseline incidence was needed to determine if an increase in cases was being detected in Canada. The national investigation was accompanied by a

rapid study to estimate the national baseline incidence of the condition prior to October 2021.

Case definitions

A national probable case definition was adapted from the WHO's definition in collaboration with provinces and territories.

Probable case definition of acute severe hepatitis of unknown origin in children:

- A person who is 16 years and younger presenting with severe acute hepatitis since October 1, 2021, requiring hospitalization

AND

- With elevated serum transaminase greater than 500 IU/L (AST or ALT)

AND

- Excluding hepatitis caused or attributed to a hepatitis virus (A, B, C, D, E) or a known or expected presentation of a drug or medication; a genetic, congenital, or metabolic condition; an oncologic, vascular, or ischemia-related condition; or an acute worsening of chronic hepatitis

Note: If hepatitis D or E serology results are pending or serology test was not done but other criteria were met, these can be reported as probable cases.

Epidemiological investigation

A national case report form was developed and shared with provinces and territories. Case report forms were completed with the data available and shared with PHAC. Case report forms included the following information:

- Demographic information (date of birth, sex, ethnicity/race)
- Current case status (status, liver transplantation)
- Illness presentation (symptoms, symptom onset dates, clinical contacts)
- Laboratory results (laboratory markers, infectious diseases, toxicology, medical investigations)
- Medical and health history (COVID-19, previous illnesses, medications, underlying medical conditions, immunosuppression, vaccination)
- Travel history (outside of Canada in the five months prior to diagnosis)
- Other information

Estimating baseline incidence

To determine whether the incident cases in the active investigation were above the baseline incidence of acute hepatitis of unknown origin in Canada, an estimate of the baseline incidence of the condition was required. Data from

the Discharge Abstract Database (DAD) were used to estimate the historical baseline incidence of acute severe hepatitis of unknown origin in children in Canada. The DAD is maintained by the Canadian Institute for Health Information (CIHI) and contains demographic, administrative and clinical information on hospital discharges in Canada. Data from the DAD are regularly shared with PHAC, making this a timely data source to support the active investigation (9). Data is submitted to CIHI by acute care facilities, regional health authorities or ministries (9). The DAD contains information from all acute inpatient facilities in Canada, with the exception of facilities in Québec (9). Data for Québec was extracted from the hospitalization files maintained at the *Ministère de la Santé et des Services sociaux* using the same methodology used to extract data from the DAD. These data were then combined with data from the DAD to estimate a nationally representative baseline.

Inclusion criteria for record extraction from the DAD were established to align as close as possible with the national probable case definition. Records were extracted for individuals 16 years of age and younger, with a primary International Classification of Diseases, Tenth Revision (ICD-10) diagnostic code indicating hepatitis not caused by hepatitis A, B, C or E. The full list of ICD-10 inclusion codes is found in **Table 1**. Extracted cases were then excluded from the analysis if a secondary or contributing diagnostic code indicated a potential known cause for hepatitis, such as a hepatitis virus. The full list of exclusionary ICD-10 codes can be found in **Table 2**. The inclusion and exclusion criteria do not fully align with the national probable case definition because of the different data collection methodologies (passive administrative data versus active case finding).

Table 1: ICD-10 codes used for inclusion of cases

ICD-10 code	Description
B17.8	Other specified acute viral hepatitis
B17.9	Acute viral hepatitis, unspecified
B19.0	Unspecified viral hepatitis with hepatic coma
B19.9	Unspecified viral hepatitis without hepatic coma
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K75.2	Nonspecific reactive hepatitis
K75.4	Autoimmune hepatitis
Z94.4	Liver transplant status

Abbreviation: ICD-10, International Classification of Diseases, Tenth Revision

Table 2: ICD-10 codes used for exclusion of cases

ICD-10 code	Description
B15.X	Acute hepatitis A
B16.X	Acute hepatitis B
B17.0	Acute delta-(super)infection in chronic hepatitis B
B17.1	Acute hepatitis C
B17.2	Acute hepatitis E
B18.X	Chronic viral hepatitis
K70.1	Alcoholic hepatitis
K73.X	Chronic hepatitis, not elsewhere classified
B25.1	Cytomegaloviral hepatitis
B58.1	Toxoplasma hepatitis
B94.2	Sequelae of viral hepatitis
P35.3	Congenital viral hepatitis
K75.3	Granulomatous hepatitis, not elsewhere classified
Z20.5	Contact with and exposure to viral hepatitis
K71.2	Toxic liver disease with acute hepatitis
Z24.6	Need for immunization against viral hepatitis
K71.3	Toxic liver disease with chronic persistent hepatitis
K71.4	Toxic liver disease with chronic lobular hepatitis
K71.5	Toxic liver disease with chronic active hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
B67.8	*Echinococcosis*, unspecified, of liver
K70.X	Alcoholic liver disease
K71.X	Toxic liver disease
K72.1	Chronic hepatic failure
K74.X	Fibrosis and cirrhosis of liver
K75.X	Other inflammatory liver diseases
K76.X	Other diseases of liver
K77	Liver disorders in diseases classified elsewhere
Z52.6	Amoebic liver abscess
C22.9	Malignant neoplasm: liver, unspecified
D13.4	Benign neoplasm: liver
S36.1	Injury of liver or gallbladder
P15.0	Birth injury to liver
Q44.6	Cystic disease of liver
B67.0	*Echinococcosis granulosis* infection of liver
B67.5	*Echinococcosis multilocularis* infection of liver
C18.3	Malignant neoplasm: hepatic flexure
T86.4	Liver transplant failure and rejection
Q44.7	Other congenital malformations of liver
Q26.6	Portal vein-hepatic artery fistula

Abbreviation: ICD-10, International Classification of Diseases, Tenth Revision

Utilizing the national dataset, the average number of cases of acute severe hepatitis of unknown origin was estimated monthly and annually. These cases were then stratified by primary diagnostic codes, which were classified as unspecified hepatitis, hepatic failure or autoimmune hepatitis. The severity of captured cases can be approximated by utilizing hospitalization data the number of severe cases. This approximation aligns with the current case definition for the outbreak investigation, which identified only cases that were hospitalized.

Incidence rates per 100,000 population were determined using the corresponding annual July 1 population estimates from Statistics Canada for people aged 16 years of age and younger (10).

A statistical comparison of the estimated national baseline of the condition and the number of cases in the current investigation was not completed. The purpose of estimating the national baseline was to determine if the number of cases in the current investigation exceeded expectation and verify the existence of an outbreak, not to determine the magnitude of the difference between the current investigation and the estimated baseline. Additional statistical testing was not completed due differences between the data collection methodology in the investigation and the methodology used for estimating the national baseline incidence.

Results

Baseline incidence

The data extracted from the DAD identified a total of 799 records meeting the inclusion criteria. After removing records that met the exclusion criteria, duplicate records and multiple discharges for the same individual, 524 unique individuals were included for analysis. These data were subsequently appended with the data shared from Québec, for a total of 704 cases included in the analysis to estimate the national baseline. A flow chart detailing the inclusion/exclusion, deduplication, and appending of data can be found in **Figure 1**.

An average of 70 (median: 71; range: 60–80) cases of acute severe hepatitis of unknown origin in children were identified per year from 2011 to 2020 in Canada (**Figure 2**). This is an average of approximately 5.83 cases per month. The average annual incidence rate of acute severe hepatitis of unknown origin is 1.14 cases per 100,000 population.

Figure 1: Flow diagram of inclusion, exclusion, deduplication, and appending of data to obtain final dataset
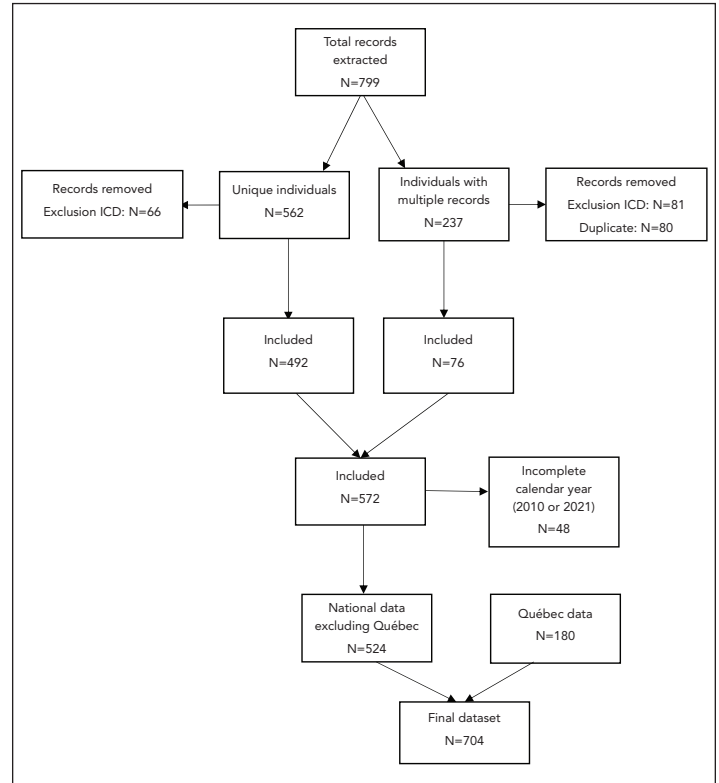
Abbreviation: ICD, International Classification of Diseases

Figure 2: Annual case counts of acute severe hepatitis of unknown origin in children under 16 years of age by diagnostic type in Canada, 2011–2020
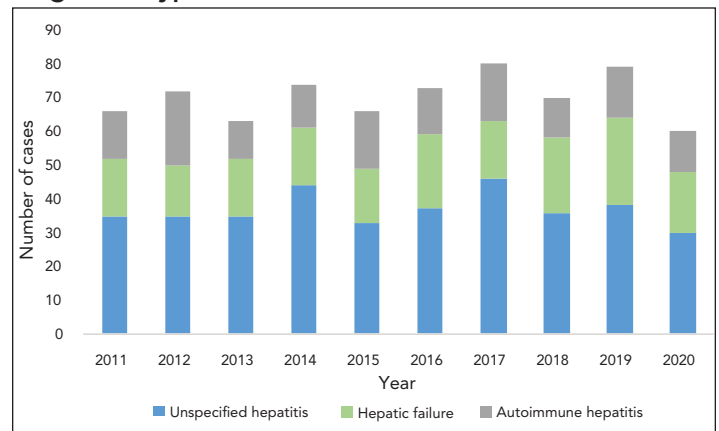
Epidemiological investigation

A retrospective and prospective investigation for cases since October 1, 2021, was started in May 2022. Provinces and territories used different methods to identify cases. All jurisdictions completed record reviews or requested health care providers to report cases. The investigation of acute severe hepatitis of unknown origin in children was closed on September 23, 2022. In Canada, 28 probable cases of acute severe hepatitis of unknown origin in children were reported to PHAC from October 1, 2021, to September 23, 2022, by six provinces: British Columbia=1; Alberta=5; Saskatchewan=1; Manitoba=3; Ontario=14; and Québec=4. The symptom onset dates for these cases were between November 3, 2021, and August 11, 2022 (**Figure 3**). The highest number of cases (n=7) was identified in April 2022 and exceeded the estimated national baseline of 5.83.

Figure 3: Number of cases of acute severe hepatitis of unknown origin in children by illness onset date, October 1, 2021 to September 23, 2022 (n=28)
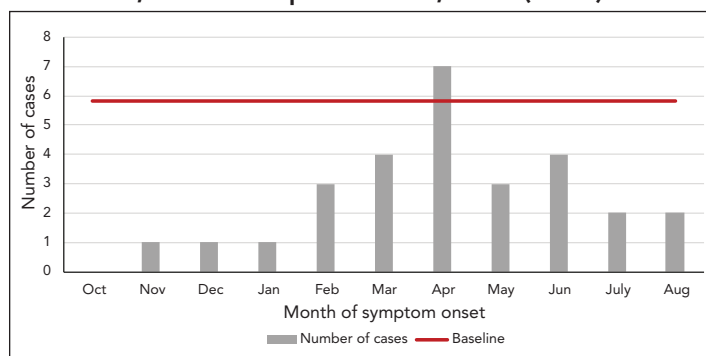
Cases identified were 1–13 years of age with a median age of 5.9 years, and 14 of 28 (50%) cases were five years of age and younger. Among the cases, 15 of 28 (54%) were male. All cases were hospitalized, and seven of 28 (25%) cases were admitted to the intensive care unit/critical care unit.

A total of five of the 26 (19.2%) cases for which testing was completed had a COVID-19 infection confirmed by a polymerase chain reaction (PCR) test during the five months prior to diagnosis (**Table 3**). One additional case reported a respiratory illness during the exposure period but was not tested for COVID-19. The SARS-CoV-2 anti-spike and/or anti-N antibody test results were available for nine cases. Of these nine cases, seven (77.8%) cases were positive and two (22.2%) cases were negative.

Adenovirus was detected in blood or respiratory samples of six of the 25 (24%) cases for which testing was completed (Table 3), with one sample typed as B7. The other cases with positive adenovirus samples were not genotyped.

Liver transplant was required for four of the 27 (14.8%) cases (Table 3); however, no significant findings related to the

Table 3: Initial epidemiological data obtained for reported cases of acute severe hepatitis of unknown origin in children 16 years and younger since October 1, 2021

Indicator	Number of cases	Total cases with testing/procedure	Percent (%)
COVID-19, confirmed by PCR	5	26	23.1
Adenovirus (blood or respiratory sample)	6	25	24.0
Liver biopsy	12	27	44.4
Liver transplant	4	27	14.8

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction

investigation (specifically, a potential cause of the hepatitis) were identified from the explant livers. Liver biopsies were completed for 12 of 27 (44.4%) cases (Table 3) and no significant findings related to the investigation or potential cause of the hepatitis were identified.

Discussion

Hospitalization data from the DAD was utilized in combination with data from Québec obtained from the *Ministère de la Santé et des Services sociaux* to estimate the number of cases that occur in Canada each year. It was estimated that an average of 70 cases of acute severe hepatitis of unknown origin in children occur each year in Canada, or 5.83 cases per month. On September 23, 2022, at the conclusion of the Canadian outbreak investigation, 28 probable cases (1–7 cases per month) had been reported in Canada from six provinces (an average of 2.3 cases per month). The number of cases exceeded baseline in April by one case, but the number of cases identified was below baseline levels for all other months. Based on these data, and despite the limitations noted below, there does not appear to have been an increase in cases of acute severe hepatitis of unknown origin in children 16 years and younger in Canada during the period of the investigation.

A Canadian national probable case definition was adapted from the WHO's case definition for the Canadian context. This definition was purposefully designed to capture as many cases as possible, some of which may have had a potential etiology for the hepatitis cases. Conversely, the Canadian case definition added additional specificity compared to the WHO definition, due to the requirement of hospitalization. Less severe cases may not have been captured if not hospitalized. Ensuring the case definition captured all possible severe cases enabled the exploration of possible etiologies, associations or causative agents of the condition. The diagnosis of acute severe hepatitis of unknown origin is not specific and does not imply that all reported cases have the same etiology.

The UK was one of the first countries to identify an increase in acute severe hepatitis in children. Recent articles have suggested potential association due to co-infection with adenovirus and AAV-2 (6,7). In the UK investigation, 63.6% of cases tested positive for adenovirus (5), whereas in Canada only 24% of cases tested positive for adenovirus. In the UK, most cases (n=214/249, 85.9%) were aged 0–5 years, whereas only 50% of Canadian cases were aged 0–5 years (7). In a recent study by Morfopoulou *et al.*, an extensive investigation involving 28 cases and 136 controls in the UK identified high levels of AAV-2 in explanted livers, and in the blood of 10 of 11 (90.1%) non-transplanted cases. The results indicated an association between AAV-2 and acute severe hepatitis in children (7). Adeno-associated virus 2 is not routinely tested for in public health laboratories: to our knowledge no Canadian samples were tested for AAV-2. The low number of adenovirus-positive cases and the differences in age demographics, together with the low number of cases in Canada, suggest that the factors leading to an increase in acute severe hepatitis cases in the UK may not have been present in Canada. In the United States, for patients under investigation with available data, approximately 10% identified active SARS-CoV-2 infection and 33% reported a history of SARS-CoV-2 infection (4). This is comparable to the Canadian cases identified, as 23.1% of Canadian cases had a COVID-19 infection confirmed by PCR in the five months prior to the diagnosis. Therefore, it is likely that the number of cases reported in Canada reflects the baseline level of acute severe hepatitis of unknown origin in children routinely observed in Canada.

Strengths and limitations

This is the first identification of a baseline incidence of acute severe hepatitis of unknown origin in children in Canada. The DAD captures administrative, clinical and demographic data from all acute care facilities or their respective health or regional ministry or department of health, with the exception of Québec (9). With the addition of the data obtained from the *Ministère de la Santé et des Services sociaux* in Québec, these data provide a nationally representative estimate of the incidence, which was not established prior to this investigation.

A limitation of this approach is the methodological differences in case classifications between: 1) estimating the national baseline incidence using passive administrative data and 2) active case finding during the investigation. Without completing a comprehensive chart review of all cases included in the baseline analysis, which was not possible due to the time constraints of an active investigation, there is potential for misclassification and reduced comparability between the cases captured in the current outbreak and in the baseline estimate. Additionally, without completing a case-by-case comprehensive medical chart review for each case included in the baseline estimate, there is the potential for misclassification and reduced comparability between the cases captured in the current outbreak and the estimate of the baseline incidence. As active case finding was

used during the current investigation, it is unlikely to have underrepresented the incidence during that period. Finally, ICD-10 diagnostic coding was used to estimate the baseline incidence but not in the investigation's case definition; thus, the cases captured in the baseline estimate may not have completely aligned with those captured in this investigation. This may have resulted in an over or under-estimation of the baseline incidence compared to the condition under investigation. However, for the purposes of this investigation, where an estimate of the national baseline incidence was rapidly required to determine if the condition being investigation was exceeding the estimated baseline number of cases, the national estimate from the DAD provided sufficient evidence to be used in conjunction with other sources of evidence to support the investigation.

For the investigation, conducting retrospective review of records for cases since October 1, 2021, was difficult to complete due to resource-intensive chart reviews, transfers of patients between facilities and jurisdictions, and different methodologies used between jurisdictions. This limits the comparability of estimates between provinces and territories, and results in potential under or overestimation of cases based on the methodology used.

Conclusion

This federal/provincial/territorial joint investigation was able to identify cases of acute hepatitis of unknown origin in Canada. The analysis of hospital records provided an estimate of the baseline incidence of acute severe hepatitis of unknown origin in children in Canada on this information, and an increase above the expected historic baseline for this condition was not observed. More research is required internationally to identify the possible cause of the increase of acute severe hepatitis in children observed in certain regions and to fully elucidate any possible links to adenovirus, AAV-2 or other potential causation.

Authors' statement

JM — Conceptualization, methodology, investigation, data analysis, original draft, review, and editing
VM — Conceptualization, methodology, investigation, data analysis, review, and editing
MH — Conceptualization, investigation, review, and editing
PLT — Data analysis
MS — Conceptualization, investigation, review, and editing
Acute Hepatitis Investigation Team — Investigation, review, and editing

Competing interests

None.

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Quantifying the economic gains associated with COVID-19 vaccination in the Canadian population: A cost-benefit analysis

Ashleigh R Tuite[1,2]*, Victoria Ng[3], Raphael Ximenes[1], Alan Diener[4], Ellen Rafferty[5], Nicholas H Ogden[3], Matthew Tunis[1]

Affiliations

[1] Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

[2] Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[3] Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, Saint-Hyacinthe, QC and Guelph, ON

[4] Policy Research, Economics, and Analytics Unit, Strategic Policy Branch, Health Canada, Ottawa, ON

[5] Institute of Health Economics, Edmonton, AB

*Correspondence:

ashleigh.tuite@phac-aspc.gc.ca

Abstract

Background: Vaccination has been a key part of Canada's coronavirus disease 2019 (COVID-19) pandemic response. Although the clinical benefits of vaccination are clear, an understanding of the population-level benefits of vaccination relative to the programmatic costs is of value. The objective of this article is to quantify the economic impact of COVID-19 vaccination in the Canadian population between December 2020 and March 2022.

Methods: We conducted a model-based cost-benefit analysis of Canada's COVID-19 vaccination program. We used an epidemiological model to estimate the number of COVID-19 symptomatic cases, hospitalizations, post-COVID condition (PCC) cases, and deaths in the presence and absence of vaccination. Median, lower and upper 95% credible interval (95% CrI) outcome values from 100 model simulations were used to estimate the direct and indirect costs of illness, including the value of health. We used a societal perspective and a 1.5% discount rate.

Results: We estimated that the costs of the vaccination program were far outweighed by the savings associated with averted infections and associated downstream consequences. Vaccination increased the net benefit by CAD $298.1 billion (95% CrI: 27.2–494.6) compared to the no vaccination counterfactual. The largest benefits were due to averted premature mortality, resulting in an estimated $222.0 billion (95% CrI: 31.2–379.0) benefit.

Conclusion: Our model-based economic evaluation provides a retrospective assessment of COVID-19 vaccination during the first 16 months of the program in Canada and suggests that it was welfare-improving, considering the decreased hospitalizations and use of healthcare resources, deaths averted and lower morbidity from conditions such as PCC.

Introduction

The availability of coronavirus disease 2019 (COVID-19) vaccines marked a turning point in Canada's pandemic response, allowing for a reduced reliance on non-pharmaceutical interventions (NPIs) to protect population health. Despite the demonstrated effectiveness of COVID-19 vaccines for preventing severe outcomes associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (1), quantifying the effect

of COVID-19 vaccination programs on Canada's pandemic trajectory is challenging. Mathematical modelling can be used to compare the Canadian pandemic experience to a counterfactual scenario of how the pandemic might have unfolded in the absence of vaccination. The modelling has shown the substantial clinical benefits of COVID-19 vaccination for preventing SARS-CoV-2 infections, hospitalizations and deaths (2,3).

Although the population impacts of COVID-19 vaccination are frequently discussed in terms of health outcomes, undertaking a cost-benefit analysis allows for a more comprehensive evaluation. In a cost-benefit analysis, all outcomes are valued in monetary terms allowing for the inclusion of non-health outcomes (4). This lens allows for a more complete accounting of the costs of illness, including reduced quality-of-life and labour market effects due to illness-associated disability and mortality, in addition to the direct healthcare costs (5). This is particularly relevant for post-COVID condition (PCC; also known as long COVID), given emerging data showing the high prevalence of PCC in countries experiencing high rates of SARS-CoV-2 infection (6,7). Additionally, there is measurable negative impact of PCC on workforce productivity, including worker absenteeism and exit from the workforce (8,9).

Initial economic evaluations of COVID-19 vaccination in North America have demonstrated that COVID-19 vaccination programs have resulted in substantial economic benefit (10,11). An analysis of Canada's vaccination program estimated a net cost-benefit of −$0.4 billion to $2.1 billion when considering treatment costs and lost productivity due to illness, and a further $27.6 billion benefit due to prevented mortality (11). Notably, this study used a statistical model that did not account for the transmissibility of SARS-CoV-2, such that the estimates of COVID-19 cases averted with vaccination are likely to be underestimated.

We used transmission modelling to retrospectively quantify the economic impact of vaccination in the Canadian population due to the prevention of SARS-CoV-2 infections, and associated hospitalizations, deaths and PCC cases. The analysis focuses on a 16-month period, following the first authorization of vaccines in December 2020 until March 2022. Over this time period, approximately 87.5% of Canadians aged five years and older had received at least one vaccine dose, 84% had completed their primary series and 48.8% had received three or more doses (12).

Methods

We conducted a cost-benefit analysis of COVID-19 vaccination in the Canadian population. We used an epidemiological model of SARS-CoV-2 transmission to assess the impact of vaccination on COVID-19 burden and evaluate the net benefit associated with vaccination.

Transmission model overview and scenarios
We adapted a previously reported age-structured agent-based model that describes the transmission of SARS-CoV-2 in the Canadian population to estimate COVID-19 cases in the presence and absence of COVID-19 vaccines (3,13). The model simulates transmission in a general community setting and excludes outbreaks in discrete settings such long-term care homes, which experienced high rates of infection. Model outputs were validated by comparison with available administrative data (3).

We developed two alternative scenarios using model parameters that were otherwise unchanged from the previously described analysis (3): a "what happened" baseline scenario and a "no vaccine" counterfactual scenario. The baseline scenario reflected the observed rollout of vaccination programs, in terms of age groups eligible for vaccination and coverage achieved (14). The model time period included the emergence of the Omicron variant of concern, which triggered an expedited rollout of third doses in the general population in the winter of 2021/2022 (15); additional details about the modelled time period are provided in Ogden et al. (3). The baseline included observed levels of NPIs over this period since the availability of vaccines did not result in the immediate removal of NPIs.

The counterfactual scenario represented what might have occurred in the absence of vaccination, with continued NPI use to mitigate recurring waves of infection and health system strain. The timing of introduction and lifting of NPIs ("shutdowns") in the counterfactual scenario was based on intensive care unit (ICU) occupancy, with thresholds based on observed ICU occupancy when NPIs were introduced in the second wave of the pandemic (September 2020 to February 2021). Because the model is stochastic, timing and duration of NPI use varied across model runs for the counterfactual scenario. In both scenarios, lifting of NPIs occurred gradually over a four-week period.

The model population size was 100,000 and outputs were rescaled to represent the size of the Canadian population. Each model scenario was run 100 times. The model was run from February 7, 2020, to March 31, 2022, and outcomes were calculated from December 14, 2020, onwards, to capture the period of divergence between the baseline and counterfactual scenarios following the start of vaccination. Model outputs included COVID-19 clinical cases (all cases experiencing symptoms, regardless of severity), hospitalizations, ICU admissions and deaths in the baseline scenario compared to the counterfactual scenario. We also calculated the number of vaccine doses administered for the baseline scenario, and number and duration of shutdowns. We used the median, lower 95% credible interval (CrI) and upper 95% CrI output values for the economic analysis.

Estimation of post-COVID condition cases averted

Model-projected clinical cases (excluding fatal cases) for the two scenarios were used to estimate the incidence of PCC following SARS-CoV-2 infection in the presence and absence of vaccination. Where possible, we used the World Health Organization case definition of PCC (16). The probability of developing PCC among clinical cases was derived from a general population cohort with age and sex-matched controls (17). We did not apply differential risks of developing PCC by age or infection severity.

Vaccination was assumed to prevent PCC two ways: first, by preventing SARS-CoV-2 infection; and second, by reducing the likelihood of developing PCC if infected. Vaccine effectiveness for preventing infection was assumed to be dependent on the predominant circulating variant of concern at the time of infection (3), while vaccine effectiveness for preventing PCC following infection was assumed to be constant (15%), regardless of the infecting variant of concern (18). Protection against PCC was only assumed among people who had received two or more vaccine doses prior to infection. We did not model a reduction in PCC risk among people vaccinated after SARS-CoV-2 infection and did not include waning of protection from PCC over the model time horizon.

Economic impact of COVID-19 cases averted

We estimated the total costs of illness, including direct and indirect costs and the value of health (morbidity and mortality) (5) to enumerate the economic impact of COVID-19 cases averted due to vaccination from a societal perspective. We used a lifetime time horizon to enumerate the costs and health consequences associated with COVID-19-attributable mortality. For PCC, we estimated costs and health effects for the first year following onset, given limited data on the longer-term trajectory of PCC. Costs are in 2021 Canadian dollars and where necessary were converted using the Canadian Consumer Price Index (19). We used a discount rate of 1.5% per year. Input parameters for the economic model were derived from the published studies, wherever possible, and by assumption and expert opinion otherwise (**Table 1**).

Table 1: Input parameters for the economic model

Applicable outcome	Parameter	Value	Source
Direct costs			
Clinical case	Net medical cost per outpatient case ($)	165.2	Tsui *et al.* (20)
	PCR test ($)	60.7	Campbell *et al.* (21)
Hospitalization (including ICU)	Healthcare cost per hospitalization ($)	25,103	CIHI (22)
PCC case	Cost per case ($, in first year)	9,683	Institute for Health Economics, *personal communication*
Vaccination	Vaccine cost per dose ($)	30	Office of the Auditor General of Canada (23)
	Administration costs per dose ($)	34	Office of the Auditor General of Ontario (24)
	Other programmatic costs per dose ($)	27	Assumption based on Sah *et al.* (10)
Indirect costs			
All	Average employment income, age 16 years and older ($)	49,095	Statistics Canada (25)
	Average employment income, ages 25–54 years ($)	58,811	Statistics Canada (25)
	Average employment income ($)	Age-specific values	Statistics Canada (25)
Productivity loss			
Clinical case	Time off work (days)	10	Government of Canada (26)
Hospitalization (including ICU)	Length of stay in hospital (days)	13	CIHI (22)
	Time from hospital discharge to return to work (days)	27	Chopra *et al.* (27)
PCC case	Proportion of PCC cases with ongoing symptoms at one year	0.15	Waters and Wernham (8)
	Average reduction in earning during first six months of illness (%)	11	Wulf Hanson (28)
	Average annual reduction in salary (%)	8.3	Extrapolated from (8) and (28)
Vaccination	Time off work to receive vaccine (days)	0.4	Government of Alberta (29)
	Proportion unable to work one day post-vaccination, dose 1	0.05	Rosenblum *et al.* (30)
	Proportion unable to work one day post-vaccination, dose 2	0.23	Rosenblum *et al.* (30)
	Proportion unable to work one day post-vaccination, booster doses	0.23	Assumption
All	Labour force participation, age 15 years and older (%)	64.6	Statistics Canada (31)
	Labour force participation, ages 25–54 years (%)	87.0	Statistics Canada (31)
	Labour force participation (%)	Age-specific values	Statistics Canada (31)

Table 1: Input parameters for the economic model (*continued*)

Applicable outcome	Parameter	Value	Source
QALY loss			
Clinical case	0–14 years	0.0050	Kirwin *et al.* (32)
	15–64 years	0.0077	Kirwin *et al.* (32)
	65 years and older	0.012	Kirwin *et al.* (32)
Hospitalization (including ICU)	QALY loss (per year)	0.58	Kirwin *et al.* (32); adjusted for length of hospital stay
	QALY loss on discharge (per case)	0.1	Kirwin *et al.* (32)
PCC case	QALY loss (1 year following discharge)	0.2937	Weighted decrement for common chronic conditions associated with PCC, Institute for Health Economics, *personal communication*
Death (net present value)	0–9 years	41.37	Kirwin *et al.* (32)
	10–19 years	37.19	Kirwin *et al.* (32)
	20–29 years	33.37	Kirwin *et al.* (32)
	30–39 years	29.4	Kirwin *et al.* (32)
	40–49 years	24.9	Kirwin *et al.* (32)
	50–59 years	20.18	Kirwin *et al.* (32)
	60–69 years	15.36	Kirwin *et al.* (32)
	70–74 years	10.35	Kirwin *et al.* (32)
	75 years	5.17	Kirwin *et al.* (32)
Vaccination	QALY loss if experience adverse event following immunization	0.00027	Sandmann *et al.* (33)
Other			
PCC case	Vaccine effectiveness for preventing PCC following infection	0.15	Al-Aly (18)
Clinical case	Percent of clinical cases developing PCC	12.7 (7.8–17.0)	Ballering (17); Thompson (34)
All	Vaccine wastage (%)	3	Office of the Auditor General of Ontario (24); for the period of December 2020 to January 2022
	Percent of cases tested by PCR	20	Statistics Canada (35) and assumption
	Discount rate (%)	1.5	CADTH (36)
	Cost per QALY threshold ($)	30,000 (20,000–100,000)	Ochalek *et al.* (37)

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CIHI, Canadian Institute for Health Information; ICU, intensive care unit; PCC, post-COVID condition; PCR, polymerase chain reaction; QALY, quality-adjusted life years

Direct costs included medical costs due to COVID-19 cases, comprising outpatient care and hospitalization for acute COVID-19 and treatment of PCC. Vaccination program costs encompassed the cost of purchasing and administering COVID-19 vaccines, including estimated wastage, as well costs associated with delivery of the program to the population, such as storage and transportation, clinic set up, and advertisement and outreach (10). The cost of wasted doses excluded vaccine administration costs.

Indirect costs included the value of lost production due to days of employment loss due to illness, disability, death or caregiving responsibilities, as well as production losses associated with time to receive a vaccine and possible adverse events following immunization (AEFI). We did not include out-of-pocket medical costs (e.g. pharmaceutical costs). Productivity loss was quantified using the human capital approach (4). We used age-specific estimates of labour force participation for the years 2020 and 2021 (31) and average employment income for 2020 (25). Caregiver costs were based on estimates of the average employment income and labour force participation of people aged 25–54 years, adjusted for estimated caregiver productivity loss (38). We included caregiver costs associated with outpatient infections in children less than 15 years of age, and caregiver costs for hospitalized cases for those age younger than 15 years and 65 years and older. To estimate production loss associated with receiving the vaccine, we used labour force participation rates and average salary in the population aged 16 and older to account for caregiver time off work to accompany children to vaccination appointments.

Health impacts included disutility from symptomatic infection, hospitalization, PCC, death and AEFI. Quality-adjusted life years (QALYs) were monetized using a cost per QALY threshold of $30,000 (37). Net benefit was estimated using the "no vaccination" counterfactual scenario as the baseline. The transmission model was constructed in AnyLogic 8 Professional 8.7.2 and the economic analysis was conducted using R (39).

Sensitivity analyses

To address uncertainty around vaccine costs, including programmatic costs, we estimated a threshold cost to determine the maximum vaccine cost per dose for which a COVID-19 vaccination would have been cost beneficial. We assumed that administration costs were fixed at the value used in the main analysis.

We explored cost per QALY thresholds values of $20,000, $50,000 and $100,000 in sensitivity analysis. We assessed lower (7.8%) and higher (17.0%) estimates of risk of PCC (34) to evaluate how these estimates impacted findings.

We re-estimated production losses using the friction cost approach. In contrast with the human capital approach, the friction cost approach assumes that after a "friction period", workers who have left the workforce will eventually be replaced by currently unemployed workers (40). We used a three-month friction period for people with PCC or who died of COVID-19 (41).

Results

With vaccination, the average Canadian population experience of the pandemic from December 2020 to March 2022 was represented in the model as a total of three shutdown periods for a total duration of 112 days. In contrast, in the absence of vaccination but with continued implementation of NPIs in the face of healthcare system strain, we would have expected four extended shutdown periods (95% CrI: 3–5) for a total duration of 343 days (95% CrI: 268–399).

Model-estimated health outcomes used for the economic analysis are presented in **Table 2** and **Figure 1**. For the median and upper bound model estimates, incidence of all COVID-19 outcomes was higher in the "no vaccine" counterfactual scenario compared to the baseline. For the lower bound model estimates, although the incidence of symptomatic infections and PCC was higher in the baseline scenario, the occurrence of hospitalizations and deaths was higher for the "no vaccination" counterfactual, due to the effectiveness of vaccination for preventing severe outcomes.

Vaccination was associated with 6.61 million (95% CrI: 0.88–10.8) QALYs gained and increased the net benefit by $298.1 billion (95% CrI: 27.2–494.6) compared to the "no vaccination" counterfactual (**Table 3**). This represents a benefit-cost ratio of 26.7 (3.6–43.3). The largest benefits were due to averted premature mortality, resulting in an estimated $222.0 billion (95% CrI: 31.2–379.0) benefit.

We estimated that if the costs of vaccination were 64 times (95% CrI: 7–104) the assumed baseline value, the vaccination program would still have provided a net benefit, when using a societal perspective that includes both direct and indirect costs. For the lower bound model estimate, this means that for a cost of up to $410 per dose (excluding administration costs), the vaccination program would be considered cost-beneficial; for the median and upper bound estimates, these values are $3,630 and $5,950 per dose, respectively. Considering direct medical costs

Table 2: Model-projected health outcomes and outcomes averted[a] in the Canadian population, December 14, 2020 to March 31, 2022

Health outcome	Scenario		Averted (counterfactual minus baseline)
	Baseline	Counterfactual (no vaccination)[b]	
Clinical cases	13,618,980 (11,709,360–15,704,590)	24,713,530 (10,327,700–30,926,840)	11,094,550 (−1,381,660–15,222,240)
Hospitalized cases (excluding ICU)	86,090 (50,930–131,510)	1,270,100 (296,480–1,880,730)	1,184,010 (245,540–1,749,220)
ICU cases	25,660 (14,440–41,810)	375,730 (86,660–590,300)	350,070 (72,220–548,480)
PCC cases	1,566,540 (1,341,560–1,815,660)	3,070,700 (1,301,046–3,823,630)	1,504,160 (−40,510–2,007,970)
Deaths	10,640 (4,180–19,770)	534,800 (83,240–819,500)	524,160 (79,060–799,730)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; PCC, post-COVID condition
[a] Median, lower and upper bounds
[b] For the counterfactual scenario, introduction of non-pharmaceutical interventions (NPIs) occurred when COVID-19 ICU occupancy exceeded three cases per 100,000 population and were implemented for an initial period of six weeks. After six weeks, NPIs were lifted if ICU occupancy was less than or equal to one per 100,000. If occupancy exceeded the one per 100,000 threshold after six weeks, NPIs were extended by four-week intervals until occupancy no longer exceeds one per 100,000. Lifting of NPIs occurred over a four-week period, with gradual removal of closures and physical distancing until reaching a return to pre-COVID-19 contact rates

Figure 1: Age distribution of COVID-19 health outcomes for the two model scenarios[a,b]
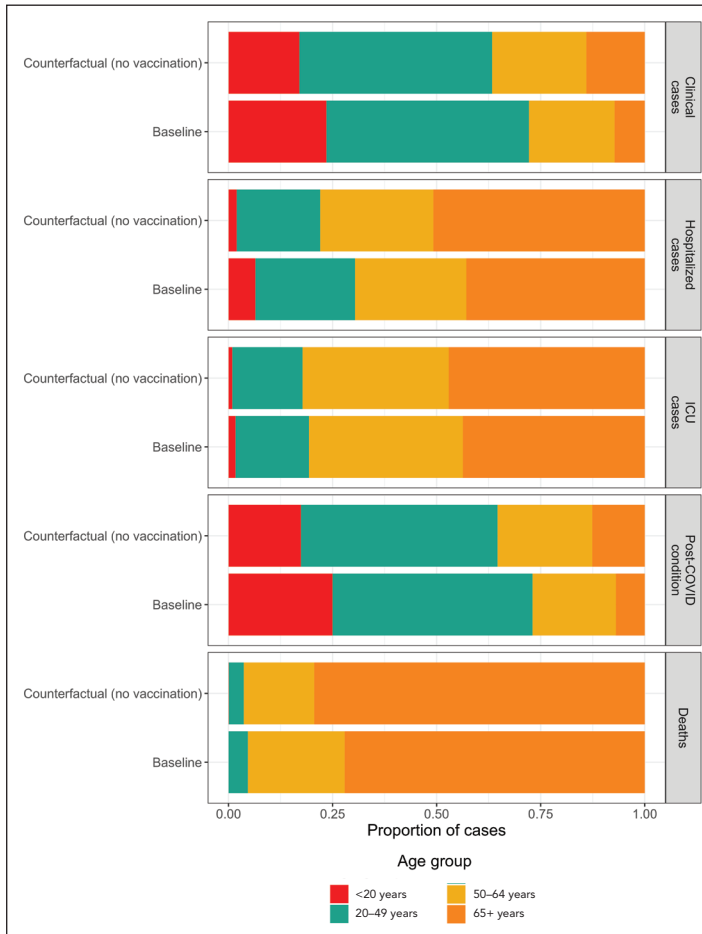
Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit
[a] The proportions of cases by age group are shown for the baseline and no vaccination counterfactual scenarios, based on median model estimates
[b] The total number of health outcomes for the two scenarios are provided in Table 2

and monetized QALYs only, which reflects the healthcare payer perspective that is typically used in healthcare decision-making, a cost per dose of up to $390, $2,910 and $4,640 would be cost beneficial for the lower, median and upper bound scenarios, respectively.

The use of higher cost per QALY thresholds increased the welfare gain of vaccination compared to the counterfactual (**Figure 2**), with a maximum benefit of $1.25 trillion for the upper bound model estimate and a threshold of $100,000 per QALY. Using a lower threshold of $20,000 per QALY and the most conservative model estimates of vaccine impact resulted in an estimated net benefit of $18.3 billion.

Lower or higher risk of PCC following infection did not have a substantial impact on estimated benefit of the vaccination program. The net benefit was estimated as $285.7 billion (95% CrI: 27.1–477.8) and $309.1 billion (95% CrI: 27.2–509.3), when PCC occurred in 7.8% or 17% of clinical cases, respectively.

Table 3: Net benefit of vaccination relative to the "no vaccination" counterfactual scenario, by health outcome and cost component

Health outcome	Incremental benefits ($ billions)		
	Direct	Indirect	Total
Clinical cases	2 (−0.176–2.77)	12.8 (−1.1–18)	14.8 (−1.28–20.8)
Hospitalized cases (including ICU)	29.6 (6.26–45.9)	10.9 (2.31–17)	40.6 (8.57–62.9)
PCC cases	14.8 (0.0342–19.8)	17.5 (0.222–23.7)	32.3 (0.256–43.5)
Deaths	N/A	222 (31.2–379)	222 (31.2–379)
Vaccination	−7.56 (−7.54–−7.59)	−4.05 (−4.04–−4.07)	−11.6 (−11.6–−11.7)
Total	38.83 (−1.426–60.88)	259.3 (28.59–433.7)	298.1 (27.16–494.6)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; N/A, not applicable; PCC, post-COVID condition

Figure 2: Net benefit associated with Canada's COVID-19 vaccination program, for different cost per quality-adjusted life year thresholds, December 14, 2020–March 31, 2022[a,b]
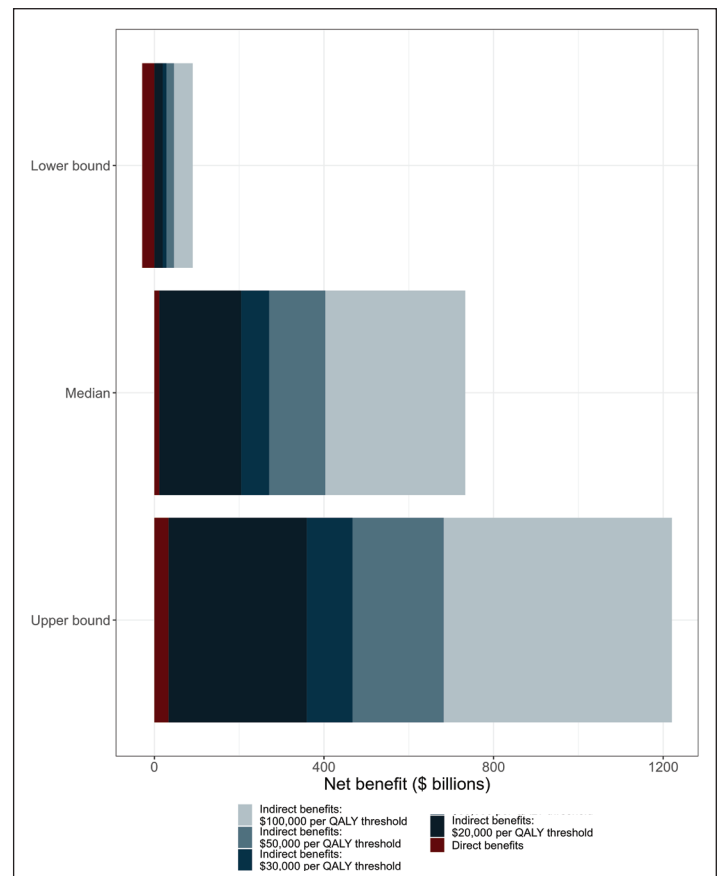
Abbreviations: COVID-19, coronavirus disease 2019; QALY, quality-adjusted life years
[a] Results are shown for lower bound, median, and upper bound model-based estimates of health outcomes averted by vaccination compared to a "no vaccination" counterfactual scenario
[b] QALYs were converted to monetary values by multiplying QALYs gained by the cost per QALY threshold. The main analysis used a threshold of $30,000 per QALY

The net benefit of vaccination was reduced when using the friction cost instead of the human capital approach to estimate production losses but remained large at $251.0 billion (95% CrI: 21.6–406.3). Most of the reduced benefit was due to lower estimated indirect costs due to mortality, a reduction of $44.4 billon (95% CrI: 5.4–84.5).

Discussion

We estimate that Canada's COVID-19 vaccination program resulted in tens to hundreds of billions of dollars in monetary benefit compared to a situation without vaccination and exclusive reliance on NPIs to control transmission. The costs of the vaccination program were far outweighed by the savings associated with averted infections and associated downstream consequences. Although the largest benefit was derived from averted premature mortality, the indirect benefit associated with reduced illness and disability was also substantial.

Our findings are consistent with an analysis of New York City's COVID-19 vaccination campaign (10). Despite different epidemiological methods and a different healthcare system, that study also demonstrated substantial cost savings associated with the city's COVID-19 vaccination program (10). A recent analysis of Canada's vaccination program also found the vaccination program to be cost-beneficial, with a net monetary benefit of −$0.4 billion to $2.1 billion, with an additional $27.6 billion in economic benefit associated with averted mortality (11); this analysis, which did not use a transmission model to estimate health outcomes averted with vaccination, likely underestimated the benefits of the program. For comparison, the 2022 analysis (11) estimated that the vaccination program prevented 30,900 deaths from January 2021 to May 2022, while our analysis estimated 524,000 deaths averted over a similar period (December 2020 to March 2022). Another model-based analysis (2) estimated 314,100 deaths averted in the first year of Canada's vaccination program (December 2020 to December 2021).

Strengths and limitations

Our estimates of benefit do not include a full accounting of the societal impact of the vaccines for speeding economic recovery (42). The counterfactual model showed that without vaccination, the number of days with NPIs in place could have been three times as high as what was observed. A recent analysis estimated that a six-month delay in access to vaccines would have resulted losses of $156 billion in economic activity (or 12.5% of Canada's gross domestic product) (11). Relatedly, we did not include the societal costs associated with the prolonged use of NPIs or the downstream effects on the healthcare system resulting from a higher burden of COVID-19 cases and deferral of care for other health needs (43,44); the inclusion of these costs would further increase the economic benefit associated with vaccination.

Due to the confidentiality of COVID-19 vaccine pricing information, we did not use or have access to these data. Instead, we used publicly available estimates of the average cost of the vaccine per dose, which may over or under-estimate the actual cost of vaccines. Similarly, information about other costs associated with the vaccination programs, including storage, transportation, outreach and wastage, were based on public information, assumption and expert opinion. Despite uncertainty in these values, we estimated that the costs of vaccination could have been 10 to 100-fold greater and still been considered a cost-beneficial intervention.

We compared the observed pandemic trajectory to a "no vaccination" counterfactual scenario where implementation of NPIs was tied to ICU capacity. The precise nature of how the pandemic might have been managed in Canada had vaccines not become available is unknowable. Notably, we did not model interventions such as continued used of masking or improvements in ventilation, which might have been more widely adopted had vaccination not become available. Given the uncertainty associated with the counterfactual, we included lower and upper bound model outputs in the economic evaluation. We also noted that vaccination remained a cost-beneficial intervention for the conservative lower bound estimate, where the model predicted higher numbers of symptomatic cases with vaccination, but reduced severe infections, compared to the counterfactual.

The benefit of vaccination for prevention of PCC remains challenging to quantify. We limited our estimates of PCC impacts in the first year following infection, given uncertainty about the longer-term trajectory of illness among cases and thus likely underestimated the total burden associated with PCC. Our model-derived estimates of PCC in the Canadian population of 4.1% (range: 3.5%–4.7%) over the modelled time period are aligned with Canadian survey data indicating that 4.6% of the Canadian population aged 18 years and older reported ongoing symptoms at least three months after SARS-CoV-2 infection, based on data collected between April and August 2022 (35). We assumed that the risk of developing PCC applied equally, regardless of severity of initial infection. The data suggested an increased risk of PCC among more severe cases (7,35) and therefore, the estimated impact of vaccination for preventing PCC may be underestimated in our model. Sensitivity analyses revealed that different assumptions about the rate of PCC are unlikely to be very influential on the costs averted by the vaccination program.

We monetized QALYs to estimate the benefits associated with averted COVID-19 morbidity and mortality. The value of statistical life (VSL) approach is an alternative for quantifying the health impacts of an intervention in cost-benefit analyses (4). The VSL allows for an accounting of the impact of reductions in mortality risk on all aspects of well-being, such as averted medical expenses and the pain and suffering associated with

illness (4). It has the disadvantage of typically not accounting for the morbidity associated with non-fatal cases (4). A comparison of VSL and monetized QALY approaches for human papillomavirus vaccination programs showed that VSL was associated with higher estimated benefit (4). Given the large burden of morbidity associated with COVID-19, we used a monetized QALY approach but note that alternate approaches may result in different estimates of the monetary benefit of COVID-19 vaccination.

Conclusion

Our model-based economic evaluation provides a retrospective assessment of COVID-19 vaccination during the first 16 months of the program in Canada and suggests that it was welfare-improving, considering decreased hospitalizations and use of healthcare resources, deaths averted and lower morbidity from conditions such as PCC. Including the benefits associated with the economic recovery through fewer days in shutdown scenarios would show even greater increases in net benefits. This analysis may help build a foundation for assessment of cost effectiveness and vaccine procurement decisions in future pandemics.

Authors' statement

ART — Conceptualization, analysis, manuscript drafting
VN — Conceptualization, modelling, manuscript review and editing
RX — Conceptualization, manuscript review and editing
AD — Conceptualization, manuscript review and editing
ER — Analysis, manuscript review and editing
NHO — Conceptualization, manuscript review and editing
MT — Conceptualization, manuscript review and editing

Competing interests

None.

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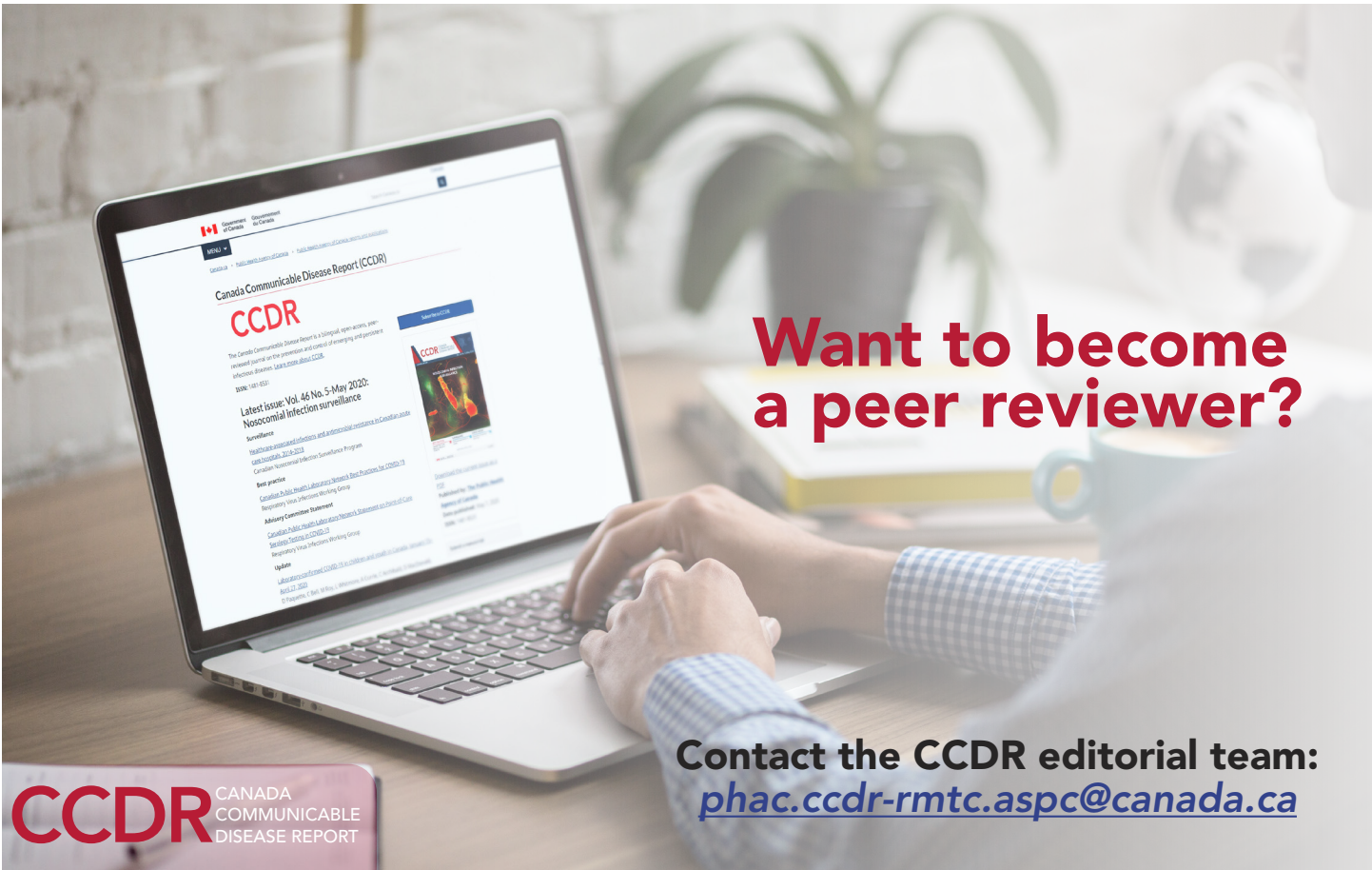
Increased PrEP uptake and PrEP-RN coincide with decreased HIV diagnoses in men who have sex with men in Ottawa, Canada

Abigail Kroch[1], Patrick O'Byrne[2,3]*, Lauren Orser[2,3], Paul MacPherson[4], Kristen O'Brien[1], Lucia Light[1], Ryu Kang[1], Agatha Nyambi[1]

Affiliations

[1] Ontario HIV Treatment Network

[2] University of Ottawa, School of Nursing, Ottawa, ON

[3] Ottawa Public Health, Ottawa, ON

[4] University of Ottawa, Faculty of Medicine, Ottawa, ON

*Correspondence:

pjobyrne@uottawa.ca

Abstract

Background: We sought to evaluate if increased uptake of HIV pre-exposure prophylaxis (PrEP) correlated to population-level changes in human immunodeficiency virus (HIV) epidemiology, in a setting with an integrated PrEP delivery system centred on a public health nurse-led PrEP clinic and referral process.

Methods: This study was conducted in Ottawa, Canada, where all positive HIV test results are reported to the public health units. Risk factor information is also collected by nurses and subsequently entered into a provincial database. We extracted these data for Ottawa from 2017 to 2021 and restricted our analyses to first-time diagnoses.

Results: We identified 154 persons with a new HIV diagnosis. Over this period, the number of new diagnoses among men who have sex with men, the group most targeted for PrEP, decreased by 50%–60%. We did not identify changes in the number of new diagnoses based on race, intravenous drug use or among women.

Conclusion: Increasing PrEP uptake in Ottawa in 2017 to 2021 coincided with a significant decrease in new HIV diagnoses among men who have sex with men. PrEP uptake in Ottawa, particularly by those most at risk, is likely supported by an integrated approach via PrEP-RN, a nurse-led public health program where individuals diagnosed with syphilis or rectal gonorrhea or chlamydia receive an automatic offer of PrEP. While these findings cannot causally link PrEP-RN or PrEP with this reduction in new HIV diagnoses, these changes in HIV epidemiology in Ottawa occurred exclusively among the group targeted for PrEP. These data highlight the efficacy and importance of PrEP.

Introduction

Beginning with the iPrEx study in 2010 (1), evidence has continued to demonstrate the efficacy of emtricitabine plus either tenofovir disoproxil fumarate (DF) (FTC/TDF) or tenofovir alafenamide (AF) (FTC/TAF) as pre-exposure prophylaxis (PrEP) to reduce the risk of human immunodeficiency virus (HIV) infection (2,3). These data led the United States Food and Drug Administration to license FTC/TDF for PrEP in 2012, with Health Canada following in 2016. In 2015, the first PrEP clinic launched in Ottawa and targeted men who have sex with men (MSM), who accounted for an estimated 77% of new HIV diagnoses in Ottawa at that time (4). Following Health Canada's approval of PrEP in 2016, two additional community PrEP clinics opened in Ottawa. The first Canadian PrEP guidelines were published in 2017 (5).

In 2018, O'Byrne *et al.* (6,7) implemented PrEP-RN, a nurse-led PrEP clinic and referral system run by public health nurses. As per provincial public health legislation (8), all positive test results for sexually transmitted infections are reported to local health

units for follow-up and contact tracing. As part of PrEP-RN, an automatic offer of PrEP was given to anyone diagnosed with infectious syphilis or rectal gonorrhea or chlamydia, or who, based on clinical assessment, was determined to be at risk of HIV infection. Between 2018 and 2021, 1,901 persons fulfilled PrEP-RN eligibility criteria and were offered a referral, of which 49% (n=845/1,736) of eligible persons accepted. Of these 845 persons who accepted PrEP, 95% (n=803) were MSM and 97% (n=820) were male.

These efforts to facilitate PrEP access—from the first clinic in 2015 to our referral system in 2018—led to an increase in the number of persons using PrEP; from 110 in 2016 to over 1,000 in 2021 (9). By 2021, this corresponded to a rate of 92/100,000 persons in Ottawa using PrEP (9). The use alone of PrEP, however, does not inform whether PrEP uptake is meeting the needs of the province and communities. To do this, it is necessary to evaluate PrEP uptake relative to HIV risk within a population. First-time diagnoses are a proxy for HIV infection and the risk experienced by the community; therefore, we examine PrEP use relative to first-time diagnoses, known as the "PrEP-to-need" ratio (10,11). The higher the ratio, the closer PrEP use is meeting the need. The PrEP-to-need ratio also allows comparison across groups and locations to understand PrEP uptake relative to need.

In Ontario, PrEP-to-need ratios have been calculated using commercial pharmacy dispensation data and first-time HIV diagnosis numbers (**Table 1**) (12). Corresponding to the reported increased PrEP use *per capita*, in Ottawa, the PrEP-to-need ratio has increased sevenfold, from five in 2017 to 35 in 2021 (9). This remains the highest in Ontario and about a third higher than the province overall, after having increased more quickly than elsewhere in Ontario (Table 1) (9). Further analyses identified that 97% of persons who use PrEP in Ontario identify as MSM, aligning with PrEP-RN outcomes of most eligible persons being MSM.

To understand the impact of our nurse-led PrEP referral and delivery network, and if the increase in the PrEP-to-need ratio in Ottawa corresponded with changes in the number of first-time HIV diagnoses, we undertook a retrospective review of first-time HIV diagnoses in Ottawa between 2017 and 2021. This period was selected because it aligned with the release of the Canadian

PrEP guidelines and preceded the implementation of PrEP-RN by 18 months.

Methods

Positive HIV test results in Ontario are reported to public health units (8), including first-time diagnoses, persons undergoing repeat or confirmatory testing, and persons who were previously diagnosed and are undergoing testing for the first time in Ontario. Public health units contact individuals with a positive HIV test to provide counselling, linkage to care and contact tracing. Public health nurses also collect demographic information, including if the individual with the reported HIV positive test result was previously diagnosed with HIV, and age, sex, country of birth and information on risk factors (e.g. sex/drug use practises). The HIV risk factors align with standard HIV data collection and include but are not limited to the following: MSM, report of injection drug use and report of heterosexual contact. Risk factors are treated independently, allowing multiple risks factors to be examined per person. These data are entered into the Integrated Public Health Information System (iPHIS).

Data collection and analysis
For positive HIV tests reported to Ottawa Public Health from January 1, 2017, to December 31, 2021, we extracted the following from iPHIS: demographic information, including age, ethnicity, sex and country of birth, risk factors, including sex of partners, drug use and prior sexually transmitted infection diagnoses, including a prior HIV diagnosis. We entered these data into a REDCap database and used SAS v.9.4 for analysis. To restrict our analysis to first-time diagnoses, we removed from the dataset any person with a recorded or reported history of an HIV diagnosis prior to their positive test in Ottawa. We assessed associations between demographic characteristics, risk factors and year of diagnosis using chi-square tests. The HIV risk factors were tested independently, as follows: male to male sexual contact versus no reported male to male sexual contact, injection drug use versus no reported injection drug use, and heterosexual contact versus no reported heterosexual contact. The HIV risk factors were not treated as mutually exclusive. Because all HIV diagnostic testing in Ontario is carried out by the Public Health Ontario Laboratories, we obtained the total number of HIV tests performed by demographic and location in the province (13).

Table 1: First-time diagnoses, PrEP uptake and PrEP-to-need ratio over time

Year of study	Ontario			Ottawa		
	First-time HIV diagnoses	PrEP users	PrEP-to-need	First-time HIV diagnoses	PrEP users	PrEP-to-need
2017	691	2,998	4.3	51	259	5.1
2018	729	6,543	9.0	43	560	13.0
2019	679	9,797	14.4	34	873	25.7
2020	508	9,584	18.9	37	862	23.3
2021	483	11,005	22.8	27	964	35.7

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; PrEP-to-need, PrEP use relative to first-time diagnoses

We calculated test positivity by dividing the number of first-time diagnoses by the number of tests in Ottawa (overall, by birth sex, and for MSM) by year (excluding prenatal tests). We analyzed trends in test positivity over time using a Cochran-Armitage test.

Results

In Ottawa, from January 1, 2017, to December 31, 2021, we identified 154 people diagnosed for the first time with HIV (Table 2). Of these, 41 new diagnoses were documented in 2017, 34 in 2018 followed by a progressive decline that levelled off to 26–27 new diagnoses per year in 2019–2021. This is a 37% decline in overall new diagnoses in 2021, compared to 2017. A chi-square test was used to determine whether diagnosis counts changed significantly over the time by demographic characteristic or HIV risk factor. The apparent decline in first-time diagnoses was significant only among men ($p<0.01$) and MSM ($p<0.05$) (Table 2). Moreover, 19 MSM were newly diagnosed with HIV in 2017, 16 in 2018, and only 5–8 diagnoses occurred in this group each year in 2019–2021, representing a 57% drop between 2017 and 2021. We did not see any significant change

in the number of new HIV diagnoses over the study period among those who reported heterosexual contact compared to those that did not ($p=0.68$), those who reported using intravenous drugs compared to those that did not ($p=0.19$) or females compared to males ($p=0.09$). We also did not identify any change in the number of first-time HIV diagnoses based on race/ethnicity (Black versus White) or age (younger than 35 years or 35 years and older) (Table 2).

As diagnoses may have been affected by decreased testing during the coronavirus disease 2019 (COVID-19) pandemic, we analyzed trends in test positivity in Ottawa over the same period. If there had been no change in the rate of HIV transmission and the decrease in new diagnoses was due to decreased testing, the test positivity rate should have remained unchanged. Here we examined test positivity overall, by birth sex and for MSM (Table 3). While there was a small decrease in the test positivity overall, from 0.07% in 2017 to 0.04% in 2021, there was a significant decrease only in men ($p<0.05$) and MSM ($p<0.01$), suggesting a true reduction in HIV transmission. We did not identify significant changes in the test positivity rate for women ($p=0.27$) (Table 3).

Table 2: Human immunodeficiency virus diagnoses over time

Demographic/risk factors	N (%)						p-value
	2017	2018	2019	2020	2021	Total	
Total	41	34	26	27	26	154	N/A
Birth sex							
Male	34 (83%)	26 (76%)	14 (54%)	16 (59%)	17 (65%)	107 (69%)	0.0899
Female	7 (17%)	8 (24%)	12 (46%)	11 (41%)	8 (31%)	46 (30%)	N/A
HIV risk factors							
MSM	19 (46%)	16 (47%)	6 (23%)	5 (19%)	8 (31%)	54 (35%)	0.049
Not MSM	22 (54%)	18 (53%)	20 (77%)	22 (81%)	18 (69%)	100 (65%)	N/A
IDU	8 (20%)	8 (24%)	1 (4%)	8 (30%)	6 (23%)	31 (20%)	0.1848
Not IDU	33 (80%)	26 (76%)	25 (96%)	19 (70%)	20 (77%)	123 (80%)	N/A
Heterosexual[a]	21 (51%)	16 (47%)	17 (65%)	19 (70%)	13 (50%)	86 (56%)	0.6822
Not heterosexual	17 (41%)	11 (32%)	9 (35%)	8 (30%)	12 (46%)	57 (37%)	N/A
Race/ethnicity							
Black	18 (44%)	6 (18%)	16 (62%)	10 (37%)	9 (35%)	59 (38%)	0.059
White	17 (41%)	22 (65%)	7 (27%)	13 (48%)	14 (54%)	73 (47%)	N/A
Other	3 (7%)	3 (9%)	1 (4%)	4 (15%)	2 (8%)	13 (8%)	N/A
Age category (years)							
Younger than 35	16 (39%)	11 (32%)	8 (31%)	12 (44%)	6 (23%)	53 (34%)	0.511
35 and older	25 (61%)	23 (68%)	18 (69%)	15 (56%)	20 (77%)	101 (66%)	N/A

Abbreviations: HIV, human immunodeficiency virus; IDU, people who reported injection drug use; MSM, men who have sex with men; N/A, not applicable
[a] Heterosexual means people who reported heterosexual contact

Table 3: Human immunodeficiency virus test positivity over time

Demographic/risk factors	Year					Trend test p-value
	2017	2018	2018	2020	2021	
Overall	0.07	0.05	0.05	0.06	0.04	0.07
Birth sex						
Male	0.11	0.08	0.05	0.07	0.04	0.002
Female	0.02	0.03	0.04	0.05	0.03	0.07
HIV risk						
MSM	0.37	0.4	0.16	0.18	0.18	0.02

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men

Discussion

We report here a significant decrease (1) in the HIV test positivity among men and MSM in Ottawa and (2) in the number of first-time HIV diagnoses in MSM from 2017 to 2021. From 2012–2016, the rolling average of new HIV diagnoses each year among MSM in Ottawa was 31.3 (range: 21–40) (14). In 2017, there were 19 new HIV infections in Ottawa in this group and in 2019–2021, this number dropped to 5–8 new diagnoses per year. Coincident with this decrease was the progressive increase in the PrEP-to-need ratio (15,16).

While we cannot prove causality, the link between increasing PrEP uptake (as evidenced by absolute increase and an increasing PrEP-to-need ratio; Table 1) and the decrease in HIV incidence in Ottawa is inferred by the fact that MSM were targeted for PrEP and it was in this group only that the number of first-time HIV diagnoses decreased. That we did not see a decrease among women or persons who use intravenous drugs, groups where PrEP uptake has been low in Ottawa and among whom PrEP was not as well targeted as part of PrEP-RN, supports the link between an increase in PrEP use and a decrease in the number of first-time HIV diagnoses. These data align with research from Australia (17), Scotland (18), Uganda and Kenya (19) and the United States (20), which have documented decreased HIV incidence after implementing high-coverage access to PrEP for MSM.

We do not believe the decreasing trend in new HIV diagnoses in Ottawa can be attributed to COVID-19 and reduced testing. First, the decrease in the absolute number of new diagnoses and in test positivity among MSM started prior to the pandemic (coincident with the launch of PrEP-RN) and was sustained over the next two years (with preliminary analyses of 2022 data showing the decrease was sustained for a third year). Second, the decrease in new diagnoses was essentially restricted to MSM, the group targeted for PrEP and where uptake was greatest. That the number of new HIV diagnoses did not change over this period for persons who use intravenous drugs or women provides a comparator group. Had decreased access to testing caused the decrease in diagnoses, one would predict a broader decrease in HIV incidence including in other demographic groups. Third, had the decrease in new diagnoses been due to decreased testing, the change in test positivity would not have shown a significant decline over the study period. Test positivity was unchanged for women, while there was a significant decrease among men, among whom MSM experienced the greatest decline.

It is equally unlikely that the outcomes we observed are related to HIV treatment (21), through which HIV-positive people can achieve undetectable viral loads and untransmittable infections (i.e. undetectable equals untransmittable, or U=U). In Ontario, Ottawa has the second-highest rate of persons living with HIV and the second-lowest rate of engagement in HIV care (22). Alternate explanations for the decreased number of new HIV infections we observed include 1) that the prevalence of HIV infection was too low for transmission to have occurred and 2) that there was no opportunity for transmission due to high levels of viral suppression among persons living with HIV. However, neither appears true in Ottawa. Without a change in testing and given that the reduction in HIV was confined to MSM, increasing PrEP uptake is the major factor that changed during our study.

Our data raise a few points for discussion. The first is the PrEP-to-need ratio and its relationship to the number of first-time HIV diagnoses. As noted, in Ottawa, the PrEP-to-need ratio increased from 5 in 2017 to 35 in 2021 (9,16) and, notably, the drop in first-time HIV diagnoses among MSM occurred in 2019 and was sustained thereafter. This raises the question of whether there is a potential PrEP-to-need threshold that coincides with substantial decreases in new HIV infections. The concept would be akin to herd immunity and represents a point where enough people use PrEP to prevent ongoing HIV transmission. If such a threshold exists, it is very unlikely to be a single target and most likely will vary depending on the transmission network and ecological context, plus whether PrEP was deployed generally or in the targeted fashion offered by PrEP-RN. Further research is absolutely required.

Second, our data suggest a potentially efficient way of addressing the initial steps of the PrEP cascade; specifically, identifying individuals at risk of HIV infection, making an offer of

PrEP and linking those who accept care. While we very strongly support increased and broad community awareness as well as increased PrEP capacity in primary care, public health units are uniquely situated to reach those individuals at greatest risk of HIV infection (23). Table 1 shows the increasing PrEP-to-need ratio in Ottawa that occurred after the implementation of targeted and systematic PrEP recommendations by public health nurses, demonstrating that the PrEP-to-need ratio increased in Ottawa faster than across Ontario, in part due to PrEP-RN implementation. Virtually all extant PrEP guidelines (4,24,25) recommend an offer of PrEP to anyone diagnosed with infectious syphilis or rectal gonorrhea or chlamydia, and to the sexual partners of someone with transmissible HIV. As studies have identified HIV diagnosis rates of 7%–8% within one year of these indicators (24), it follows that HIV incidence would decrease after a public health unit implemented a program that offered PrEP to those meeting these criteria. This is made possible by the fact that all positive sexually transmitted infection results are reported to public health units in Ontario. This creates a feasible, high-yield strategy with a potentially low number-needed-to-treat. Further, that the decrease in HIV diagnoses in this study was observed in MSM reinforces the validity of the indicator criteria by showing how targeted recommendations for, and provisions of, PrEP can coincide with decreases in the number of first-time HIV diagnoses among MSM at the population level.

Third, despite the apparent benefits of using the current indicator criteria for initiating PrEP among MSM, our findings support criticisms highlighting a lack of emphasis on HIV risk factors for people who use injection drugs and for heterosexual exposures, which disproportionately affects Black and Indigenous Peoples, potentially exacerbating existing health disparities for these groups (26–30). Furthermore, evidence has shown that risk factors do not correlate directly across groups, with Black MSM experiencing a greater risk of HIV transmission, while reporting fewer risk factors than White counterparts (30). Our findings, which showed a significant decrease in new HIV diagnoses among MSM but not for other groups, support this criticism. While PrEP-RN was not exclusively restricted to MSM, it did in effect target these men as current guidelines for PrEP (4,25–27) best serve these men, thus enabling this population to experience a greater uptake of PrEP. Concerted efforts are now required to determine PrEP indicators for other populations, thus enabling other groups to benefit from the potential population-level effects we observed among MSM in Ottawa.

Limitations
First, our data were based on reported positive HIV test results, which relies on people accessing testing. Among those with new diagnoses, time may have passed since transmission occurred, so temporality is difficult to establish. However, this is not a new limitation of HIV epidemiology and the sustained decrease in diagnoses suggests a decline in HIV incidence. Second, COVID-19 became widespread in 2020 and so the decreased number of new HIV diagnoses could have resulted from reduced

sexual activity or testing. Since we observed these decreases beginning in 2019, we think this is unlikely. It is equally unlikely that COVID-19 would have affected changes in the PrEP-to-need ratio exclusively in Ottawa, compared to across Ontario (see Table 1). Third, our data regarding risk factors was based on self-report to public health nurses, although this has been the historical approach to data collection for HIV epidemiology, and so would not have manifested as a change in our data compared to those preceding them. Nonetheless, because the variables in our analysis were limited to the data collected by public health nurses, there were potential confounders or effect modifiers not examined in this analysis. Lastly, our data arose from one city in Canada without comparison. It is possible that the decreases in new diagnoses are related to influences that we have yet to identified. While possible, to the best of our knowledge, there were no other major changes related to, or interventions targeted at, HIV, MSM or other at-risk populations in Ottawa during the look-back period. We also know there were no changes in the uptake of HIV treatment or in levels of viral suppression in our region during this time. Our data also show a comparison in PrEP-to-need ratios across Ontario, identifying a faster increase in PrEP uptake in Ottawa in conjunction with PrEP-RN implementation.

Conclusion
We report here on a significant decrease in the number of first-time HIV diagnoses and in HIV test positivity in Ottawa from 2017 to 2021 among MSM, coincident with increased PrEP uptake within this group (as evidence by increasing PrEP-to-need ratios in Ottawa). While our results cannot show causality, decreased diagnoses occurring only in the groups targeted for PrEP (men and MSM) suggests a relationship. As the reduction in HIV diagnoses was first noted in 2019, and because the HIV test positivity rate dropped for MSM but no other group, we do not believe the effect was the result of COVID-19 or changes in access to healthcare. We also note that as the PrEP-to-need ratio increased from 2017 to 2021 (primarily among MSM), the greatest decrease in new HIV diagnoses occurred in 2019. While our analyses highlighted the utility of using the PrEP-to-need ratio as part of understanding overall PrEP uptake and HIV diagnosis numbers, a question for ongoing research is the possibility that there is a PrEP-to-need threshold that must be reached to prevent HIV transmission. Finally, the focus on individuals with a diagnosis of syphilis or rectal gonorrhea or chlamydia as most in need of PrEP potentially restricted the benefits of this intervention to MSM. Future work needs to elucidate guidelines for people who use injection drugs and those with heterosexual risk factors that account for differential population-level risk, with the specific intent to improve health equity for Black and Indigenous Peoples. While our results emerge from small numbers, they nevertheless constitute important data on the key role public health units can play in the initial steps of the PrEP cascade, the strength of existing criteria to identify those who would benefit from PrEP, and the need to better understand HIV risk in other populations. Indeed, these

results provide a proof-of-concept that systematically offering PrEP may lead to a decrease in HIV incidence in MSM, driven by the targeting of PrEP to high-risk persons. This is part of public health follow-up for infectious syphilis, rectal gonorrhea and chlamydia, as it was done for PrEP-RN. With such ongoing efforts, PrEP will no doubt reduce ongoing HIV transmission, improving both individual and population health.

Authors' statement

Competing interests

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Older adults and non-response to rabies post-exposure prophylaxis: Challenges and approaches

Reed Morrison[1,2], Cindy Nguyen[1], Monir Taha[1], Robin SL Taylor[1]*

Abstract

Rabies vaccines are highly effective and immunogenic in most populations, including when used as rabies post-exposure prophylaxis (RPEP); however, there is mounting evidence that the immune response to rabies vaccines, though predicted to be adequate, may be lower in older adults. Despite this, there are no specific recommendations in Canadian guidance to monitor the serological response of older adults following RPEP. Furthermore, while Canadian guidance recommends the intramuscular route for RPEP vaccination, there is good evidence supporting the immunogenicity, effectiveness and safety of RPEP vaccination using the intradermal route. We present a case of an 87-year-old male with rabies exposure who failed to respond to two series of RPEP with intramuscular rabies vaccination but responded to a third series using intradermal vaccine administration and provide reasoning for subsequent management. This case is brought forward to prompt discussion and research as to the utility of completing serology in older adults receiving RPEP as well as vaccination strategies, including route of administration, in those who do not respond to an initial course of RPEP vaccination.

Affiliations

[1] Ottawa Public Health, Ottawa, ON

[2] Public Health and Preventive Medicine program, University of Ottawa, Ottawa, ON

*Correspondence:

robin.taylor1@ottawa.ca

Introduction

Public health professionals and clinicians in primary and emergency care commonly engage in risk assessment and management of potential rabies exposures. In Ottawa alone, a city of approximately 1 million persons, 1,305 rabies investigations were completed by Ottawa Public Health (OPH) in 2019, which resulted in 227 recommendations for rabies post-exposure prophylaxis (RPEP). Despite the regularity of managing potential rabies exposures, little attention is given to more complex cases such as RPEP non-responders. We present a case of an 87-year-old male with rabies exposure who failed to respond to two series of RPEP and provide reasoning for subsequent management.

Human rabies is rare in Ontario, with the last domestic case occurring in 1967. However, due to continued circulation in wild animal reservoirs and the near-certain mortality of the disease, rabies remains an important public health concern. Rabies disease is caused by viruses of the *Lyssavirus* genus, of which rabies virus (RABV) is the type species. In Canada, wild mammals such as bats, skunks, racoons and foxes are the reservoirs of

RABV. RABV can be transmitted to humans through the saliva of an infected animal. While this is most often due to a bite, exposure of non-intact skin or mucosal surfaces to rabies virus-containing saliva can also result in infection (1).

Symptoms develop following an incubation period of 3–8 weeks, although this may be as short as a few days or as long as several years. Once symptoms develop, a prodrome characterized by apprehension, excitability, headache, non-specific sensory changes and fever can last between two and 10 days. The disease then progresses to an acute neurological phase consisting of encephalomyelitis and cardiac failure that is nearly always fatal, even when medical care is provided (1).

Case

The patient was an 87-year-old male living in a long-term care home (LTCH). Informed consent to share his case was provided by his substitute decision maker. His comorbidities included type 2 diabetes mellitus, Parkinson's disease, dementia, sinus bradycardia, orthostatic hypotension and malnutrition as

evidenced by low serum protein and knowledge of his dietary intake. The patient was not previously vaccinated against rabies.

During an evening in the spring of 2021, the patient was observed by staff to come into direct (skin) contact with a bat that had entered the LTCH. The patient informed staff that the bat was in contact with his left index finger. Staff noted small wounds on the skin in that area with no visible bite marks. Immediately following exposure to the bat, the patient's wounds were cleaned with saline.

The bat was captured by LTCH staff and delivered to animal control for rabies testing. Ottawa Public Health was notified of the exposure at this time. A rabies risk assessment was performed in consultation with staff at the LTCH. Due to the high-risk exposure, it was recommended that the patient receive RPEP consisting of body-weight-based rabies immunoglobulin (RabIg) and a vaccination series. Ottawa Public Health was notified three days later that the bat had tested positive for RABV, which meant completing the full RPEP series was indicated.

Post-exposure prophylaxis
Rabies post-exposure prophylaxis is provided to individuals following a confirmed rabies exposure. The Canadian Immunization Guide (CIG) provides guidance regarding the risk assessment for rabies following exposure to potentially rabid animals. Post-exposure prophylaxis or testing of a bat is generally recommended after direct contact with a bat because it is very difficult to ensure that a bite did not take place (2).

Rabies post-exposure prophylaxis for unimmunized persons consists of providing immediate passive immunity immunization through RabIg and eliciting active immunity immunization through a rabies vaccination series. Immunocompetent individuals are recommended to receive a series of four 1.0 mL intramuscular (IM) doses of an approved vaccine on days 0, 3, 7, and 14. Immunocompromised individuals receive an additional dose on day 28. There are two vaccine preparations approved for use in Canada: the inactivated human diploid cell rabies vaccine (HDCV) and the inactivated purified chick embryo cell rabies vaccine (PCECV) (2).

The IM route is the only recommended route of vaccine administration for RPEP in the CIG (2). Conversely, the World Health Organization recommends either the IM or intradermal (ID) route for RPEP, noting that many clinical trials have confirmed immunogenicity, effectiveness, and safety of RPEP using the ID route (3). A recent statement by the Ontario Immunization Advisory Committee notes that, within Canada, British Columbia and Alberta are the only provinces to have implemented a recommendation for the ID route of RPEP. The statement recommends that the "rabies vaccine for post-exposure prophylaxis should continue to be provided using

the IM route of administration in Ontario at this time." While recognizing evidence of safety and effectiveness of the ID route, the statement highlights epidemiologic, logistical, and cost considerations for their recommendation (4).

Case, revisited
Following convention, the date RPEP begins is "day 0", and all events that follow are calculated in days following RPEP initiation. All vaccination doses, routes and serology results are summarized in **Table 1**.

The patient received 15% of the total body weight-based RabIg (KamRAB™ human rabies immunoglobulin) dose in the left deltoid the morning following exposure (day 0) and the remaining 85% in the left index finger and left deltoid on day 1 (an insufficient dose of RabIg provided to the patient on day 0 necessitated a further dose the next day to achieve an adequate weight-based dosage). The patient received a total RabIg dose of 20 IU/kg as per CIG recommendations.

In accordance with guidelines, a four-dose series of PCECV (RabAvert®) vaccine was given IM on days 0, 3, 7, and 14 in the right deltoid.

Ottawa Public Health routinely recommends serology 7–14 days following an RPEP series for those 70 years of age and older due to a lack of compelling literature evidence demonstrating adequate serological response in that age group. As such, due to the patient's age, blood for serology was drawn 11 days after the fourth vaccine dose. Results showed no detectable rabies antibodies (Table 1).

Given the initial non-response, and in accordance with CIG recommendations, a second series consisting of five doses of HDCV (IMOVAX® Rabies) was delivered IM on newly established days 0, 3, 7, 14, and 28. Multiple repeated serological determinations showed no detectable antibodies (Table 1). The inadequate serological response was hypothesized to be due primarily to the patient's advanced age with possible contribution of malnutrition (*personal communication with treating physician, n.d.*). Ottawa Public Health consulted the respective vaccine manufacturers and no deficiencies in effectiveness with the associated lot numbers were identified. Similarly, consultation with laboratory colleagues revealed a high level of confidence in the results. A cold chain failure is an unlikely contributing factor as OPH supplied the vaccine directly to the LTCH and there were no noted gaps in the cold chain. Lastly, administration error is also unlikely as OPH provides teaching on administration of rabies vaccines as part of standard practice.

Table 1: Summary of vaccination and serology results

Date	Day #/Series	Product	Administration route	Dose	Serology results[a]
2021-05-24	Day 0	Rabies Immunoglobulin (Human) (KamRAB™)	IM left deltoid	15% of total[b]	N/A
2021-05-24	Day 0/Series 1	PCECV (RabAvert®)	IM right deltoid	1 mL	N/A
2021-05-25	Day 1	Rabies Immunoglobulin (Human) (KamRAB)	Wound infiltration left index finger and IM left deltoid	85% of total[b]	N/A
2021-05-27	Day 3/Series 1	PCECV (RabAvert)	IM right deltoid	1 mL	N/A
2021-05-31	Day 7/Series 1	PCECV (RabAvert)	IM right deltoid	1 mL	N/A
2021-06-07	Day 14/Series 1	PCECV (RabAvert)	IM right deltoid	1 mL	0.0 IU/mL
2021-06-18	Day 25	N/A	N/A	N/A	0.0 IU/mL
2021-06-22	Day 0/Series 2	HDCV (IMOVAX® Rabies)	IM left deltoid	1 mL	N/A
2021-06-25	Day 3/Series 2	HDCV (IMOVAX Rabies)	IM right deltoid	1 mL	N/A
2021-06-29	Day 7/Series 2	HDCV (IMOVAX Rabies)	IM right deltoid	1 mL	N/A
2021-07-06	Day 14/Series 2	HDCV (IMOVAX Rabies)	IM right deltoid	1 mL	N/A
2021-07-09	Day 17	N/A	N/A	N/A	0.0 IU/mL
2021-07-19	Day 27	N/A	N/A	N/A	0.0 IU/mL
2021-07-20	Day 28/Series 2	HDCV (IMOVAX Rabies)	IM right deltoid	1 mL	N/A
2021-08-07	Day 46	N/A	N/A	N/A	0.0 IU/mL
2021-08-12	Day 0/Series 3	HDCV (IMOVAX Rabies)	ID right and left deltoid areas	0.1 mL x 2=0.2 mL	N/A
2021-08-15	Day 3/Series 3	HDCV (IMOVAX Rabies)	ID right and left deltoid areas	0.1 mL x 2=0.2 mL	N/A
2021-08-19	Day 7/Series 3	HDCV (IMOVAX Rabies)	ID right and left deltoid areas	0.1 mL x 2=0.2 mL	N/A
2021-09-03	Day 22	N/A	N/A	N/A	1.28 IU/mL

Abbreviations: HDCV, human diploid cell rabies vaccine; ID, intradermal; IM, intramuscular; N/A, not applicable; PCECV, purified chick embryo cell rabies vaccine
[a] Listed by the day of blood draw
[b] Dose in mL is not provided to protect personal health information

Based on literature review and in consultation with expert colleagues, OPH and the patient's substitute decision maker decided to proceed with a third series of RPEP vaccination using the ID route. The patient received 0.1 mL ID of HDCV (IMOVAX Rabies) in the skin overlying each of the right and left deltoids (total 0.2 mL) on newly established days 0, 3, and 7. Blood for serology drawn 15 days after the final vaccine dose was reactive at 1.28 IU/mL.

Effectiveness and immunogenicity

The rabies vaccine is highly effective and immunogenic in most populations. In the context of RPEP, evidence suggests that close to 100% of healthy individuals will have an adequate antibody response within 14–30 days of finishing a vaccination series (2,5–7). Real-world treatment failures are extremely rare and are often due to deviations from accepted RPEP protocols (8). There have been no documented RPEP failures in Canada (2).

Despite overall high immunogenicity, there are some populations that are more likely to demonstrate lower antibody responses. Those with immunosuppression, and particularly those with very low CD4 counts, are at the highest risk of not seroconverting

following vaccination (9). There is also mounting evidence that the immune response to rabies vaccines may be lower in older adults (9). For example, a recent meta-analysis found that adults older than 50 years of age had lower maximal mean antibody titres following an RPEP regimen. Although maximal mean titres were protective (higher than 0.5 IU/mL), there were lower rates of seroconversion in those older than 50 years of age when compared to those younger than 50 years (7). Similarly, pre-exposure prophylaxis studies (10,11) have found an age-based gradient of decreasing immunogenicity and seroconversion. Additional studies on pre-booster antibody titres have also found an age-based gradient (12).

Unfortunately, there is a research gap regarding the immunogenicity of the rabies vaccine in adults older than 70 years of age. A robust literature search strategy conducted for this article identified a single case series that separately analyzed the data of individuals older than 70 years of age. This study compared the antibody titres of different age groups, including 10 individuals older than 70 years of age, and did not find an age-based difference (13).

Monitoring rabies post-exposure prophylaxis response

Because the rabies vaccine is highly immunogenic and effective in most populations, there are very few circumstances when the CIG recommends serology following RPEP. In immunocompetent persons, serology is recommended 7–14 days after completing an RPEP series only when there has been "substantial deviation" from the recommended schedule or a non-recommended vaccine has been used (2).

The CIG recommends serology 7–14 days after a five-dose RPEP series in immunocompromised persons (2). Despite evidence suggesting a lower immune response in older adults to rabies vaccines, older age is not considered an immunocompromising risk factor in the CIG; therefore, there are no specific recommendations for monitoring serology in older adults following RPEP. While this is consistent with some pieces of guidance including that of the World Health Organization (3), French guidance (14) does suggest completing serology following a course of RPEP in older adults.

If there has been an inadequate antibody response to vaccination, a second series of vaccination is recommended along with further serological testing. The CIG does not provide further vaccination guidance if the second RPEP vaccination series does not produce an adequate antibody response, stating instead that "some immunocompromised people may never mount an appropriate immune response" (2). A review of the published and grey literature also could not identify any relevant guidance documents or statements that provide direction following an inadequate serological response to two complete RPEP series.

The British HIV Association (15) provides suggestions for patients with human immunodeficiency virus (HIV) who fail to seroconvert after an initial RPEP regimen, which are potentially instructive for other non-responders (including multiple non-responders after multiple vaccine series). They propose that these individuals should be offered double-dose and/or more frequent vaccine doses and should be considered for a combination of ID and subcutaneous routes during a subsequent RPEP vaccination series. Similar strategies have also been used in HIV-negative immunocompromised patients (16).

Discussion

This case is unique as it is the first published instance of an individual demonstrating serological response to the ID route of vaccination for RPEP following a non-response to the IM route. This is important as very little is known about changing the route of administration of RPEP vaccination. A recent systematic review identified just two studies on the topic (17). Based on the limited evidence, the authors concluded that changing the route of administration either during a course of RPEP or between a pre-exposure prophylaxis series and a RPEP series was a safe and effective way to achieve a serological response. The review did not identify any previous research on changing routes of administration between RPEP vaccination series, as this case discusses.

This case is also unique in demonstrating an adequate serological response after a third series of RPEP vaccination. Previous research has found that those who do not respond to an initial course of RPEP almost uniformly respond following additional doses (16,18). Rarely, chronic non-responders, usually with severe immune suppression, have been identified and do not seroconvert regardless of re-vaccination strategy (2,19).

The patient's adequate serological response following ID vaccination may reflect the skin's important role in the immune system and specifically the higher concentration of antigen-presenting cells in the skin (8). It may also have been a function of a higher cumulative total vaccine dose. It is unclear if this patient would have seroconverted sooner had we attempted other strategies during the second round of RPEP such as administration of vaccine using the ID route, "double dosing" or more frequent dosing, although these strategies are not addressed in the CIG.

Conclusion

Given how frequently potential rabies exposures are managed, it is important for clinicians and public health practitioners to be aware of approaches to complex cases such as RPEP non-responders. This case prompts three considerations for public health practice. First, due to the life-threatening nature of the disease, we believe it is medically prudent to complete serology in adults 70 years of age and older following each RPEP series until new research can more confidently describe the nature of the immune response of older adults to rabies vaccination. Second, we contend that clinicians may consider the circumstances under which a different route of vaccine administration would benefit those who do not respond to an initial RPEP series. Lastly, given that neither the CIG nor other guidance documents identified during a literature review provide case management advice for individuals who fail to seroconvert following two RPEP vaccination series, we recommend that further research and guidelines be developed to address this gap.

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Surveillance for *Ixodes scapularis* and *Ixodes pacificus* ticks and their associated pathogens in Canada, 2020

Christy Wilson[1]*, Salima Gasmi[2], Annie-Claude Bourgeois[1], Jacqueline Badcock[3], Justin Carr[4], Navdeep Chahil[5], Heather Coatsworth[6], Antonia Dibernardo[6], Priya Goundar[7], Patrick Leighton[8], Min-Kuang Lee[5], Muhammad Morshed[5,9], Marion Ripoche[10], Jade Savage[11] on behalf of eTick, Hanan Smadi[3], Christa Smolarchuk[12], Karine Thivierge[13,14], Jules Koffi[2]

Affiliations

*See full list of affiliations in the Appendix

*Correspondence:

christy.wilson@phac-aspc.gc.ca

Abstract

Background: *Ixodes scapularis* and *Ixodes pacificus* ticks are the principal vectors of the agent of Lyme disease and several other tick-borne diseases in Canada. Tick surveillance data can be used to identify local tick-borne disease risk areas and direct public health interventions. The objective of this article is to describe the seasonal and spatial characteristics of the main Lyme disease vectors in Canada, and the tick-borne pathogens they carry, using passive and active surveillance data from 2020.

Methods: Passive and active surveillance data were compiled from the National Microbiology Laboratory Branch (Public Health Agency of Canada), provincial and local public health authorities, and eTick (an online, image-based platform). Seasonal and spatial analyses of ticks and their associated pathogens are presented, including infection prevalence estimates.

Results: In passive surveillance, *I. scapularis* (n=7,534) were submitted from all provinces except Manitoba and British Columbia, while *I. pacificus* (n=718) were submitted only from British Columbia. No ticks were submitted from the Territories. The seasonal distribution of *I. scapularis* submissions was bimodal, but unimodal for *I. pacificus*. Four tick-borne pathogens were identified in *I. scapularis* (*Borrelia burgdorferi*, *Anaplasma phagocytophilum*, *Babesia microti* and *Borrelia miyamotoi*) and one in *I. pacificus* (*B. miyamotoi*). In active surveillance, *I. scapularis* (n=688) were collected in Ontario, Québec and New Brunswick. Five tick-borne pathogens were identified: *B. burgdorferi*, *A. phagocytophilum*, *B. microti*, *B. miyamotoi* and Powassan virus.

Conclusion: This article provides a snapshot of the distribution of *I. scapularis* and *I. pacificus* and their associated human pathogens in Canada in 2020, which can help assess the risk of exposure to tick-borne pathogens in different provinces.

Introduction

Ixodes scapularis and *Ixodes pacificus* ticks can transmit several bacterial, viral and protozoan pathogens to humans (1). The geographic range and population of *I. scapularis* is increasing in southern central and eastern Canada (2,3), due to climate and environmental changes that have enhanced habitat suitability for ticks in more areas (4,5). These changes can further alter tick behaviour and extend their periods of activity, which can increase exposure to tick-borne diseases (TBD) (1,6). To reduce the burden from TBD, the continued range expansion of ticks in Canada must be met with increased capacity for and awareness of TBD prevention and surveillance (1). Tick surveillance data inform the environmental risk of Lyme disease (LD), which can guide public health authorities in targeting prevention and control efforts and support LD diagnostics by healthcare professionals (7).

The causative agent of LD, *Borrelia burgdorferi*, is transmitted by *I. scapularis* in central and eastern Canada and by *I. pacificus* in British Columbia. Reported incidence of LD in people has increased more than 10-fold (from 144 to 1,615 cases) from 2009 to 2020 (8). Additional TBD, transmitted by *I. scapularis* or *I. pacificus,* are emerging in Canada; including anaplasmosis (9), babesiosis (10), hard tick-borne relapsing fever (11) and Powassan virus disease (12).

Passive tick surveillance has been used since the 1990s to identify *I. scapularis* and *I. pacificus* tick populations and the presence of tick-borne pathogens (13,14). Active tick surveillance began in the 2000s to detect areas with established tick populations where LD risk may become endemic (LD risk areas) (15). Efforts to summarize passive and active tick surveillance annually at the national level began in 2019 (16), providing a baseline for TBD risk that over time will facilitate the identification of current trends and enable the projection of future trends.

The objective of this surveillance report is to summarize the geographic and seasonal characteristics of the main LD vectors in Canada, *I. scapularis* and *I. pacificus*, collected through passive and active surveillance in 2020. This article will also summarize the prevalence and spatial distribution of their associated human pathogens.

Methods

Data sources
This report uses two types of surveillance data from ten different providers. Passive tick surveillance data was provided by the National Microbiology Laboratory (NML) Branch of the Public Health Agency of Canada (PHAC), British Columbia Centre for Disease Control (BCCDC), Alberta Health, Saskatchewan Ministry of Health, and eTick. Active tick surveillance data were provided by Thunder Bay District Health Unit, Kingston, Frontenac

and Lennox & Addington Public Health, *Laboratoire de santé publique du Québec*, New Brunswick Department of Health and New Brunswick Provincial Veterinary Laboratory.

Passive tick surveillance
Passive tick surveillance is the voluntary submission by the public of ticks (or their images) to medical or veterinary clinics, regional public health authorities or other institutions (e.g. university laboratory) for species identification and laboratory testing (13). This analysis was limited to *I. scapularis* and *I. pacificus* ticks collected within Canada in 2020, although several other tick species were also identified. Ticks could be submitted at any point during the year. Ticks with a location of acquisition outside of Canada, with a submitter's history of travel to another province, or from within Canada but could not be geocoded were excluded. Ticks were submitted individually (single submission) or in groups of two or more (multiple submission). Provinces with five or fewer ticks submitted for species identification and laboratory testing were excluded from the study to avoid misinterpretation of results. No ticks were submitted from Northwest Territories, Nunavut or Yukon as no passive surveillance programs exist for *I. scapularis* and *I. pacificus*.

Since 2009, regional passive tick surveillance programs have been gradually discontinued in several jurisdictions (e.g. Nova Scotia, southwestern Québec and eastern Ontario) dependent on laboratory capacity and as *I. scapularis* populations have become established. However, ticks (or their images) acquired in these jurisdictions could be submitted by the public directly to NML or to eTick.

eTick is a validated, web-based, community-science passive surveillance system for tick identification (17). Individuals submit images of ticks they encounter to the online platform, which are then examined by trained personnel for species identification. The system began in 2017 in Québec, with five additional provinces added by 2020 (Saskatchewan, Ontario, Newfoundland and Labrador, New Brunswick and Nova Scotia). Similar to provincial tick surveillance data sources, eTick collects information on location of acquisition, date of collection, submitter travel history, tick host, tick species and tick instar. All ticks from eTick were classified as single submissions, as users must upload images of each tick individually.

Ticks acquired and submitted in Saskatchewan, Ontario, Québec, Newfoundland and Labrador, New Brunswick, Nova Scotia and Prince Edward Island were tested for *A. phagocytophilum*, *B. burgdorferi*, *B. miyamotoi* and *B. microti* at NML or University of Saskatchewan using the methods previously described (16,18). Ticks from BCCDC were tested only for *B. burgdorferi* and *B. miyamotoi* (14). Laboratory results for ticks from Alberta Health were not available. Specimens from tick records

submitted through eTick were not routinely requested for testing of tick-borne pathogens but could be forwarded onto a laboratory for this purpose at the request of local public health authorities.

Active tick surveillance

In active surveillance, ticks are collected from the environment using drag sampling or by capturing host mammals that are then examined for ticks. This analysis used *I. scapularis* ticks collected during drag sampling from 7 sites in Ontario, 24 sites in Québec and 14 sites in New Brunswick. Drag sampling takes place in late spring/summer (May through July) and fall (September through November), with some sites visited during both periods.

All ticks were tested at NML for *A. phagocytophilum*, *B. microti*, *B. burgdorferi*, *B. miyamotoi* and Powassan virus. Ticks were collected and tested using the methods previously described (16,18,19).

Analysis

Tick characteristics

For passive surveillance, descriptive statistics were calculated for submission type (sample-based or image-based), tick species, province of acquisition, instar (larva, nymph, adult female or adult male), level of engorgement (unfed or engorged), host (human, dog, cat or other) and month of collection. Where date of collection was not available, the date the sample was received was used to ascertain the month of collection. For active surveillance, descriptive statistics were calculated for province of collection and instar (larva, nymph, adult female or adult male). All data were cleaned and analysed in R (version 4.0.2).

Ticks that were acquired in Canada in passive surveillance were mapped using QGIS (version 3.8.1) based on their location of

acquisition, except for ticks from Alberta that were mapped to the centroid of the forward sortation area (the first three characters of the postal code) of acquisition. Ticks from submitters with a history of travel in the previous 14 days within the same province as the locality of acquisition were geocoded to the location of exposure during travel. Ticks from submitters with multiple travel locations listed were not mapped. In active surveillance, the location of tick dragging was geocoded and mapped.

Infection prevalence

To account for pooled testing of ticks from some jurisdictions for passive surveillance, maximum likelihood estimates (MLE) of prevalence were calculated in Excel (version 16.0) with 95% confidence intervals (CI) using the PooledInfRate add-in (version 4.0) (20,21). This estimates the probability of infection for an individual tick in the population using the results of testing of the pooled samples (i.e. a group of one or more ticks submitted and tested together). Co-infection prevalence was calculated among single submissions only to ascertain true co-infections; that is, two or more pathogens in a single tick. Where ticks were not tested in pools, prevalence was the number of positive ticks divided by the number of ticks tested.

Results

Passive surveillance tick characteristics

In 2020, a total of 8,252 ticks were submitted from nine provinces (**Table 1**, **Figure 1**). Ticks from Manitoba were excluded as five or fewer ticks were submitted. No ticks were submitted from Northwest Territories, Nunavut or Yukon. The majority (71.49%) of ticks were sample-based submissions (n=5,899) and the remainder were image-based submissions (n=2,353). Ticks from Ontario and Québec comprised 77.24% of all ticks submitted.

Table 1: Number of *Ixodes pacificus* and *Ixodes scapularis* ticks collected through passive surveillance by province, Canada, 2020

| Province	Tick species (number of ticks)			Type of surveillance (number of ticks)[a]		Type of submission (number of submissions)[b]	
	Ixodes pacificus	*Ixodes scapularis*	Total	Sample-based	Image-based	Single submissions	Multiple submissions
British Columbia	718	0	718	718	N/A	670	22
Alberta	0	81	81	81	N/A	81	0
Saskatchewan	0	12	12	7	5	12	0
Ontario	0	5,139	5,139	3,713	1,426	4,964	68
Québec	0	1,235	1,235	809	426	1,208	12
Newfoundland and Labrador	0	14	14	4	10	14	0
New Brunswick	0	646	646	516	130	634	6
Nova Scotia	0	392	392	36	356	392	0
Prince Edward Island	0	15	15	15	N/A	13	1
Total	718	7,534	8,252	5,899	2,353	7,988	109

Abbreviation: N/A, not applicable
[a] Sample-based submissions are physical tick specimens; image-based submissions are images submitted to eTick
[b] Single submissions consist of one tick; multiple submissions consist of two or more ticks submitted together by the same individual

Figure 1: *Ixodes pacificus* and *Ixodes scapularis* ticks submitted through passive tick surveillance, Canada, 2020[a]
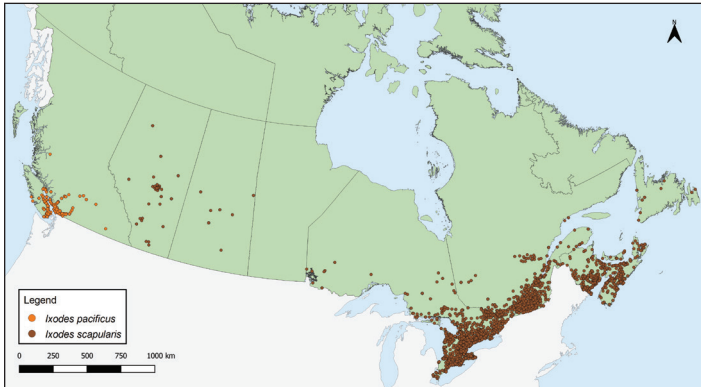
[a] Each dot represents the probable location of acquisition for an *I. pacificus* (n=718) or *I. scapularis* (n=7,397) tick submitted through passive surveillance. Ticks from Alberta Health were mapped to the centroid of the forward sortation area (first three characters of the postal code) of acquisition. One hundred and thirty-seven ticks were not mapped because the probable location of acquisition could not be determined

The majority (96.80%) of ticks were from single submissions, but there were 109 multiple submissions (range: 2–6 ticks per submission; median: 2).

Tick instar, level of engorgement and host were available for 100% of *I. pacificus*. Tick instar, level of engorgement and host were available for 89.66%, 67.60% and 99.92% of *I. scapularis*, respectively. The majority of ticks submitted were adult female ticks (*I. pacificus*: 97.21%; *I. scapularis*: 92.36%) (**Table 2**). Adult males, nymphs and larvae were submitted less frequently. Overall, 8.91% of *I. pacificus* and 41.76% of *I. scapularis* were engorged. Humans were the most common host among *I. pacificus* and *I. scapularis* (90.39% and 82.98%, respectively) followed by dogs (8.91% and 13.34%, respectively).

Month of acquisition and tick instar was available for 100% of *I. pacificus* and 89.66% of *I. scapularis*. (**Figure 2**). Adult *I. scapularis* ticks submitted peaked in May and October through November, while adult *I. pacificus* submitted peaked only in May. Only 0.14% of *I. pacificus* submitted were nymphs, while 4.20% of *I. scapularis* submitted were nymphs, peaking in June. Larvae of *I. scapularis* (0.13%) were submitted June through September; no *I. pacificus* larvae were submitted.

Passive surveillance infection prevalence

Data on laboratory testing were available for 98.27% of *I. pacificus* and 98.20%–98.40% of *I. scapularis* from sample-based submissions, depending on pathogen. The most prevalent pathogen was *B. burgdorferi*, detected in 17.19% of *I. scapularis* (95% CI: 16.17–18.26) (**Table 3**). Other tick-borne pathogens (*A. phagocytophilum*, *B. microti* and *B. miyamotoi*) and co-infections were estimated to have a prevalence rate of less than 1%. Among *I. pacificus*, only *B. miyamotoi* was identified (0.14%, 95% CI: 0.01–0.68).
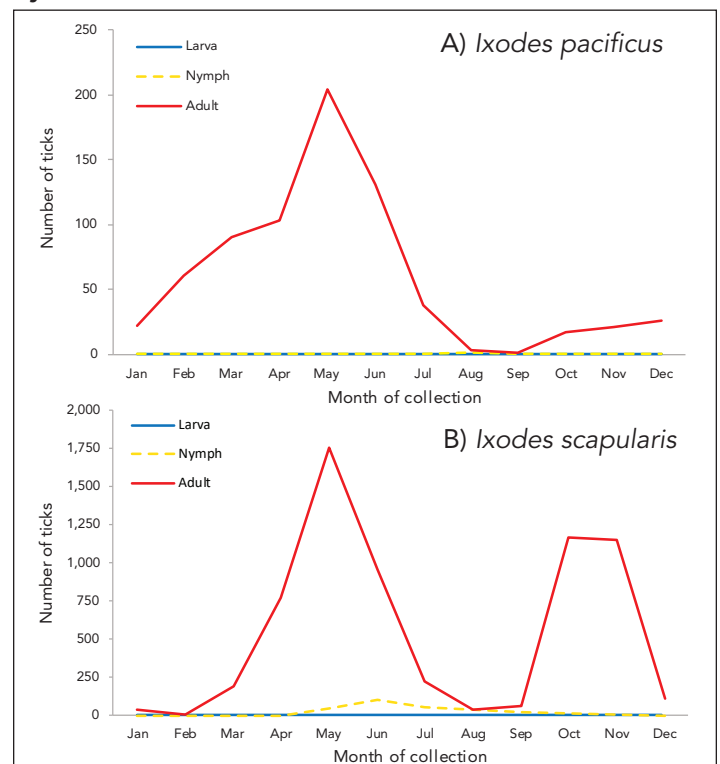
Table 2: Instar, level of engorgement and host of *Ixodes pacificus* and *Ixodes scapularis* ticks submitted through passive surveillance, Canada, 2020[a]

Characteristics	Tick species			
	Ixodes pacificus		*Ixodes scapularis*	
	n	%	n	%
Instar				
Larva	0	0	9	0.13
Nymph	1	0.14	284	4.20
Adult female	698	97.21	6,239	92.36
Adult male	19	2.65	223	3.30
Total	718	100	6,755	100
Level of engorgement				
Engorged	64	8.91	2,127	41.76
Unfed	654	91.09	2,966	58.24
Total	718	100	5,093	100
Host				
Human	649	90.39	6,247	82.98
Dog	64	8.91	1,004	13.34
Cat	3	0.42	132	1.75
Other[b]	2	0.28	145	1.93
Total	718	100	7,528	100

[a] Data are presented for all ticks where available, regardless of whether the tick was part of a single or a multiple submission
[b] Includes environment, horse, rabbit and other unspecified animal

Figure 2: Number of *Ixodes pacificus* and *Ixodes scapularis* ticks submitted through passive surveillance, by month and tick instar, Canada, 2020[a]

[a] Data are presented for *I. pacificus* (n=718) and *I. scapularis* (n=6,755) ticks submitted through passive surveillance. Month of submission or tick instar was not available for *I. scapularis* (n=779)

Table 3: Prevalence of *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia burgdorferi* and *Borrelia miyamotoi* infection in *Ixodes pacificus* and *Ixodes scapularis* ticks submitted through passive surveillance, Canada, 2020[a,b]

Pathogen	Infection prevalence			
	Ixodes pacificus		*Ixodes scapularis*	
Single agent	Maximum likelihood estimate			
	%	95% CI	%	95% CI
Anaplasma phagocytophilum	N/A	N/A	0.87	0.64–1.15
Babesia microti	N/A	N/A	0.02	0–0.09
Borrelia burgdorferi	0	0–0.54	17.19	16.17–18.26
Borrelia miyamotoi	0.14	0.01–0.68	0.49	0.33–0.71
Total single agent	0.14	0.01–0.68	18.21	17.16–19.29
Co-infection	Co-infection rate			
	%	Number co-infected ticks/ number ticks tested	%	Number co-infected ticks/ number ticks tested
Anaplasma phagocytophilum + *Babesia microti*	N/A	N/A	0	0/4,874
Anaplasma phagocytophilum + *Borrelia burgdorferi*	N/A	N/A	0.12	6/4,874
Anaplasma phagocytophilum + *Borrelia miyamotoi*	N/A	N/A	0.02	1/4,874
Babesia microti + *Borrelia burgdorferi*	N/A	N/A	0	0/4,882
Babesia microti + *Borrelia miyamotoi*	N/A	N/A	0	0/4,883
Borrelia burgdorferi + *Borrelia miyamotoi*	0	0/705	0.14	7/4,882
Total co-infected	0	0/705	0.29	14/4,883

Abbreviations: CI, confidence interval; N/A, not tested
[a] All *I. pacificus* (n=718) were not tested for *A. phagocytophilum* and *B. microti*. All *I. scapularis* from Alberta or submitted through eTick were not tested for any pathogen
[b] Number of *I. scapularis* ticks tested: *A. phagocytophilum* (n=5,090), *B. microti* (n=5,100), *B. burgdorferi* (n=5,098), *B. miyamotoi* (n=5,094). Number of *I. pacificus* ticks tested: *B. burgdorferi* (n=705), *B. miyamotoi* (n=705)

Prevalence of *B. burgdorferi* was higher in multiple submissions of *I. scapularis* (32.31%, 95% CI: 25.27–40.34) than from single submissions (16.71%, 95% CI: 15.69–17.78). Infection prevalence did not differ significantly by submission type for any other pathogen. *Ixodes scapularis* submitted from human hosts did not have significantly different infection prevalence compared to *I. scapularis* submitted from non-human hosts.

Tick-borne pathogens were largely found in southern and eastern Ontario, southern Québec and southern New Brunswick (**Figure 3**, **Figure 4**, and **Table 4**). *Borrelia burgdorferi*-infected *I. scapularis* were found in six provinces: Saskatchewan, Ontario, Québec, Newfoundland and Labrador, New Brunswick and Nova Scotia. Three quarters of *B. burgdorferi*-infected *I. scapularis* submissions were within previously identified LD risk areas (74.88%; 644/860). Lyme disease risk areas are localities in which there is evidence of reproducing populations of known tick vector species (particularly *I. scapularis* and *I. pacificus*) and the likely transmission of *B. burgdorferi* (22). Most multiple submissions came from LD risk areas (76.15%; 83/109), of which 51.81% were infected with *B. burgdorferi* (43/83).

Figure 3: *Ixodes scapularis* ticks submitted through passive surveillance infected with *Borrelia burgdorferi*, Canada, 2020[a,b]

Legend
● *Borrelia burgdorferi*
▨ Lyme disease risk area

0 200 400 600 800 km
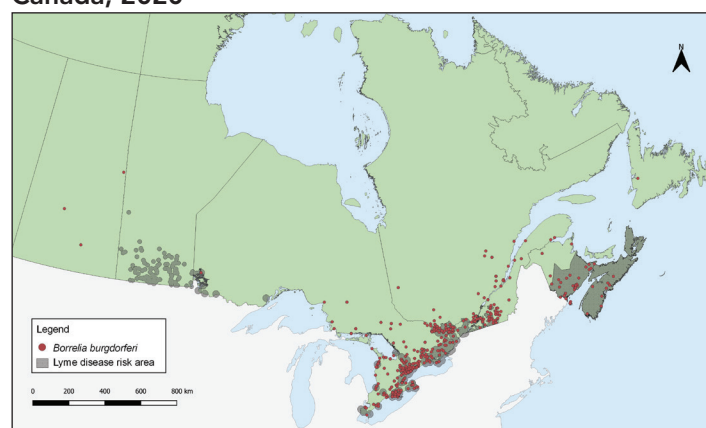
[a] Each dot represents the probable location of acquisition of at least one *I. scapularis* (n=860) single or multiple tick submission submitted through passive surveillance that was infected with *B. burgdorferi*. Eight ticks were not mapped because the probable location of acquisition could not be determined
[b] Lyme disease risk areas are identified by the provinces as of 2021 using the methods described in the 2016 national Lyme disease case definition (22). On the map, risk areas are identified as hatched gray areas

Figure 4: *Ixodes pacificus* and *Ixodes scapularis* ticks submitted through passive surveillance infected with *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi* and co-infections, Canada, 2020[a]
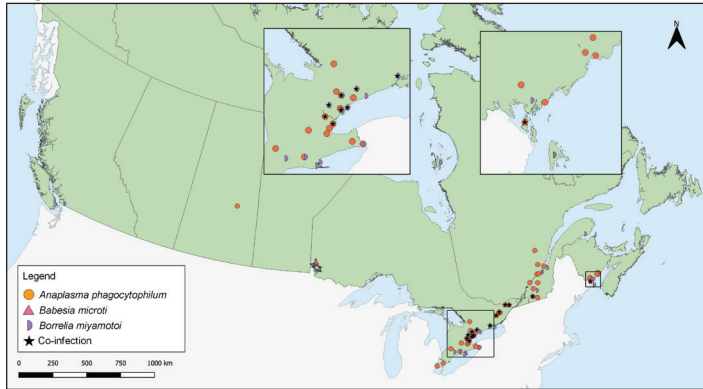
[a] Each symbol represents the probable location of acquisition of an *I. pacificus* (n=1) or *I. scapularis* (n=67) single or multiple tick submission submitted through passive surveillance that tested positive for *A. phagocytophilum* (n=42), *B. microti* (n=1), *B. miyamotoi* (n=25) or a co-infection (n=14). Co-infections were limited to only single submissions of ticks and include *B. burgdorferi* + *B. miyamotoi* (n=7), *B. burgdorferi* + *A. phagocytophilum* (n=6) and *A. phagocytophilum* + *B. miyamotoi* (n=1) all in *I. scapularis*. Two ticks with *A. phagocytophilum* and one tick with *B. miyamotoi* were not mapped because the probable location of acquisition could not be determined

Anaplasma phagocytophilum was found in *I. scapularis* (0.87%) in four provinces: Saskatchewan, Ontario, Québec, and New Brunswick (Figure 4, Table 4). *Borrelia miyamotoi* was found in British Columbia, Ontario, Québec and New Brunswick. *Babesia microti* was found only in Ontario. Co-infections were found in Ontario, Québec and New Brunswick.

Active surveillance tick characteristics
In 2020, *I. scapularis* (n=688) were collected in three provinces in active surveillance: New Brunswick (n=445), Ontario (n=128) and Québec (n=115). Adult males (n=264/688; 38.37%) and females (n=214/688; 31.10%) were collected most often, followed by nymphs (n=209/688; 30.38%) and larva (1/688; 0.15%).

Active surveillance infection prevalence
Laboratory testing results were available for 99.27% of *I. scapularis*. The most prevalent pathogen was *B. burgdorferi* (29.28%), present in Ontario, Québec and New Brunswick (**Table 5**). *Anaplasma phagocytophilum* (4.54%) was found in ticks in Ontario and New Brunswick. The remaining pathogens were found in less than 0.5% of *I. scapularis*: three *B. miyamotoi*-positive and one *B. microti*-positive ticks were found in New Brunswick, and one tick with Powassan virus (deer tick lineage) was found in Québec. The site locations where *I. scapularis* was collected in active surveillance are shown in **Figure 5**.

Table 4: Prevalence of *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia burgdorferi* and *Borrelia miyamotoi* infection in *Ixodes scapularis* and *Ixodes pacificus* ticks submitted through passive surveillance, by province, Canada, 2020[a]

Province	Infection prevalence Maximum likelihood estimate							
	Anaplasma phagocytophilum		*Babesia microti*		*Borrelia burgdorferi*		*Borrelia miyamotoi*	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Ixodes pacificus								
British Columbia	N/A	N/A	N/A	N/A	0	0–0.54	0.14	0.01–0.68
Ixodes scapularis								
Alberta	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Saskatchewan	14.29	0.85–51.51	0	0–35.43	42.86	12.96–77.51	0	0–35.43
Ontario	0.73	0.49–1.04	0.03	0–0.13	17.78	16.56–19.04	0.46	0.28–0.72
Québec	1.24	0.63–2.19	0	0–0.47	19.50	16.87–22.35	0.62	0.23–1.36
Newfoundland and Labrador	0	0–48.99	0	0–48.99	25.00	1.52–73.74	0	0–48.99
New Brunswick	1.17	0.48–2.40	0	0–0.74	8.97	6.72–11.68	0.58	0.15–1.57
Nova Scotia	0	0–9.64	0	0–9.64	25.00	13.03–40.81	0	0–9.64
Prince Edward Island	0	0–20.15	0	0–20.15	0	0–20.15	0	0–20.15
Total	0.87	0.45–1.15	0.02	0–0.09	17.19	16.17–18.26	0.49	0.33–0.71

Abbreviations: CI, confidence interval; N/A, not tested
[a] Number of ticks tested: British Columbia (n=705), Alberta (n=0), Saskatchewan (n=7), Ontario (n=3,705–3,713), Québec (n=809), Newfoundland and Labrador (n=4), New Brunswick (n=514–516), Nova Scotia (n=36), Prince Edward Island (n=15)

Table 5: Infection prevalence of *Ixodes scapularis* ticks collected in active surveillance, by province, Canada, 2020

| Province | Infection prevalence | | | | | | | | | |
| | *Anaplasma phagocytophilum* | | *Babesia microti* | | *Borrelia burgdorferi* | | *Borrelia miyamotoi* | | Powassan virus | |
	Proportion positive tick[a]	%	Proportion positive tick	%	Proportion positive tick	%	Proportion positive tick	%	Proportion positive tick	%
Ontario	2/128	1.56	0/128	0	53/128	41.41	0/128	0	0/128	0
Québec	0/110	0	0/110	0	40/110	36.36	0/110	0	1/110	0.91
New Brunswick	29/445	6.52	1/445	0.22	107/445	24.04	3/445	0.67	0/445	0
Total	31/683	4.54	1/683	0.15	200/683	29.28	3/683	0.44	1/683	0.15

[a] Proportion positive tick equals the number of positive ticks divided by the number of ticks tested

Figure 5: *Ixodes scapularis* ticks with associated pathogens collected through active surveillance, Canada, 2020[a,b]
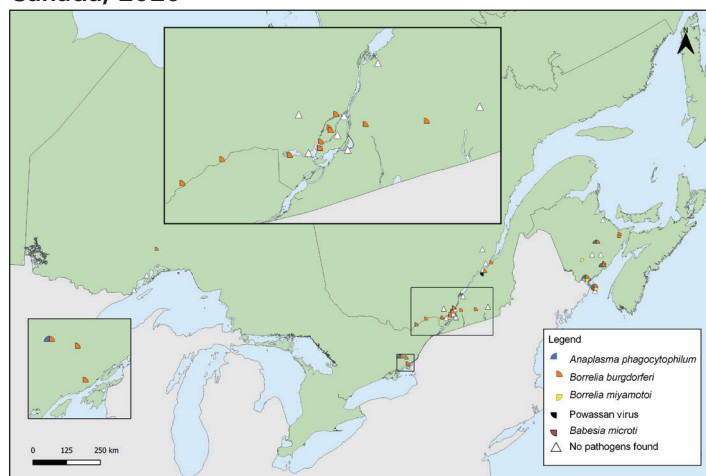
[a] Each symbol represents an active surveillance site where *A. phagocytophilum* (n=31), *B. microti* (n=1), *B. burgdorferi* (n=200), *B. miyamotoi* (n=3), or Powassan virus (n=1) were found in *I. scapularis* ticks. There were 17 sites where no tick-borne pathogens were identified in *I. scapularis* ticks
[b] Number of ticks tested: Ontario (n=128), Québec (n=110) and New Brunswick (n=445)

Discussion

In 2020, *I. scapularis* and *I. pacificus* were submitted in passive surveillance from nine provinces. Only *I. pacificus* were submitted in British Columbia. The majority of ticks were female adults and obtained from human hosts. Among ticks that were tested, 18.21% of *I. scapularis* and 0.14% of *I. pacificus* were infected with at least one tick-borne pathogen, mainly *B. burgdorferi*. In active surveillance, five tick-borne pathogens (*A. phagocytophilum*, *B. burgdorferi*, *B. miyamotoi*, *B. microti* and Powassan virus) were identified among the *I. scapularis* collected in Ontario, Québec and New Brunswick.

From passive surveillance, 5,899 ticks were sample-based submissions, a decrease of 44% from the 10,549 ticks submitted in 2019 (16), which could be due, in part, to impacts from the coronavirus disease 2019 (COVID-19) pandemic. Beginning in spring 2020, COVID-19 pandemic restrictions affected traditional passive surveillance, as health units, medical clinics and veterinary clinics were limited in their ability to accept physical tick specimens at some locations (e.g. Simcoe Muskoka District Health Unit) (23). The decrease in submissions could also be due to changes to sample-based submission programs and greater emphasis on image-based submission programs in most jurisdictions. Active surveillance was also affected by pandemic restrictions, as in-person activities like field surveillance were limited (e.g. *Institut national de santé publique du Québec*) (24). Data from the Canadian Lyme Sentinel Network, which was included in the 2019 report (16), was unavailable in 2020 as Canadian Lyme Sentinel Network activities were suspended (*personal communication, C. Guillot, 2022*).

In passive surveillance, ticks were submitted every month, but submissions followed distinct species-specific patterns influenced by location and weather. Despite fewer ticks submitted to passive surveillance than in 2019 (16), the same bimodal peaks for *I. scapularis* adults that have been shown historically in central and eastern Canada (13,25–27) were observed in 2020. For *I. pacificus*, a single springtime peak was observed as shown previously in British Columbia (14,16) and the western United States (28). While risk of exposure to ticks was present year-round, exposure to tick-borne pathogens is dependent on infection prevalence and attachment time.

The proportion of ticks submitted from dogs or cats increased from 8.9% in 2019 to 15.1% in 2020 (16). This increase is likely from including data from eTick: whereas sample-based passive surveillance programs in some localities (e.g. health units, municipalities) are restricted to ticks from human hosts only, image-based passive surveillance has no such restriction, leading to a greater proportion of ticks from animal hosts when eTick data was included in this report.

Compared to 2019 (16), province and pathogen-specific infection prevalence estimates were similar, but geographic distribution was more limited in some cases (e.g. *I. scapularis* with *A. phagocytophilum* were limited to only the southernmost parts of New Brunswick compared to 2019). Several factors influence infection prevalence estimates from year-to-year or between

provinces, including annual variation in weather, surveillance effort, habitat suitability, presence of established vector and reservoir populations and interactions between humans, ticks and the environment. Because of small sample sizes tested (n=<10), infection prevalence estimates from Saskatchewan and Newfoundland and Labrador should be interpreted with caution.

Ixodes pacificus (found in British Columbia) historically have low rates of *B. burgdorferi* infection (14,16), while *B. burgdorferi* infection prevalence in *I. scapularis* found in central and eastern Canada is typically higher (18,25,29); both trends continued to be observed in 2020. Jacob *et al.* (30) report higher infection prevalence among companion animals of several tick-borne pathogens compared to our estimates; however, participating veterinary clinics in that study were skewed towards areas with higher or emerging risk of TBD, likely leading to overestimation of the province-level infection prevalence. The one-year study also concluded in spring 2020, thus not accounting for the effects of pandemic restrictions on tick exposure for the remainder of 2020.

The majority of *B. burgdorferi*-infected *I. scapularis* had probable location of acquisition within LD risk areas (8,22). The remaining *B. burgdorferi*-infected *I. scapularis* may be adventitious ticks carried by migrating birds or mammals (15) or collected from areas with emerging LD risk. Provinces routinely review LD risk areas based on new surveillance data according to the 2016 case definition (22).

Despite limited opportunities for active field surveillance due to ongoing COVID-19 pandemic restrictions, over 600 *I. scapularis* were collected in drag sampling from 45 sites across Ontario, Québec and New Brunswick. Five tick-borne pathogens were identified, ranging in prevalence from 0.15% to 29.28%. This was the first detection of Powassan virus (deer tick lineage) in active surveillance in Québec (24), which has previously been identified in small numbers of *Ixodes* spp. in Manitoba, Ontario and New Brunswick (12,31).

In addition to single-agent infection with *B. burgdorferi* and the four other tick-borne pathogens, three distinct types of co-infections were identified. Surveillance beyond LD for other TBD is warranted to monitor the emergence and spread of these pathogens, especially as suitable habitat for *Ixodes* spp. is predicted to increase due to changes in climate and environment (1,32,33).

Co-infections have been reported to varying extents in ticks found in Canada (16,18) and the United States (34). Humans who are co-infected may experience a greater number and duration of symptoms compared to single-agent infections (35,36). Many factors influence the risk of co-infection, including attachment time, but preventing tick bites can help prevent transmission of all TBDs.

Strengths and limitations

This article presents a snapshot of infection prevalence and range estimates for the main LD vectors in Canada. While traditional passive surveillance programs have been discontinued or limited to specific hosts in some regions, incorporating data from eTick allows broader geographic and host representation from these regions in this summary. Combining passive and active surveillance also allows the strengths and weaknesses of the systems to complement each other. For example, while active surveillance is limited in geographic and temporal scope, passive surveillance programs gather data from large areas throughout the year.

There are several limitations to this study. Due to competing public health priorities, passive surveillance programs and the effort of active surveillance vary across Canada. As previously noted, COVID-19 pandemic restrictions affected public health services and surveillance in 2020, resulting in fewer sample-based submissions to passive surveillance and active surveillance that was less geographically representative compared to the previous year (16). Shifts in passive tick surveillance programs (e.g. limits on tick host or location of acquisition of tick; discontinuation of regional or provincial programs) have also limited the number of submissions. While digital platforms like eTick offer timely tick identification, tick specimens are not routinely requested for tick-borne pathogen testing from imaging identification platforms (17). Recall bias in reporting locality of acquisition and travel history in passive surveillance might create uncertainty as to the exact location where ticks were found. Finally, there are likely other active surveillance programs conducted in 2020 not included here in this summary if ticks were not sent for pathogen testing at NML. Furthermore, the number of larvae included in active surveillance is an underestimate, since our dataset only includes ticks sent for testing, for which larvae are rarely sent. These underestimates of the number of ticks may affect the accuracy of infection prevalence of various pathogens.

Conclusion

Ixodes scapularis and *I. pacificus* were identified across Canada in passive and active surveillance, some of which were infected with *B. burgdorferi*, the LD pathogen, but also with emerging tick-borne pathogen(s). Healthcare professionals and the public should be aware that there is a risk of exposure to infected ticks outside of known LD risk areas, even if the risk is low in those areas. The identification of new tick-borne pathogens in several jurisdictions in active surveillance may help public health authorities update their prevention strategies, as some of those emerging tick-borne illnesses, like Powassan virus disease, may have infection transmission patterns that differ from LD. As climate change alters the habitat and seasonality of tick vectors, continued surveillance can help in timely identification of new risk areas for LD and other emerging TBD, and directing public health interventions towards these at-risk areas.

Authors' statement

Competing interests

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Appendix: List of affiliations

[1] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

[2] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Saint-Hyacinthe, QC

[3] Public Health New Brunswick, New Brunswick Department of Health, Fredericton, NB

[4] New Brunswick Provincial Veterinary Laboratory, Department of Agriculture, Aquaculture and Fisheries, Fredericton, NB

[5] BCCDC Public Health Laboratory, BC Centre for Disease Control, Vancouver, BC

[6] National Microbiology Laboratory Branch, Public Health Agency of Canada, Winnipeg, MB

[7] Ministry of Health, Regina, SK

[8] Epidemiology of Zoonoses and Public Health Research Group (GREZOSP), Faculty of Veterinary Medicine, Université de Montréal, Saint-Hyacinthe, QC

[9] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC

[10] Institut national de santé publique du Québec, Montréal, QC

[11] Bishop's University, Sherbrooke, QC

[12] Analytics and Performance Reporting Branch, Health Standards, Quality and Performance Division, Alberta Health, Edmonton, AB

[13] Laboratoire de santé publique du Québec, Sainte-Anne-de-Bellevue, QC

[14] Institute of Parasitology, McGill University, Sainte-Anne-de-Bellevue, QC

CCDR
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