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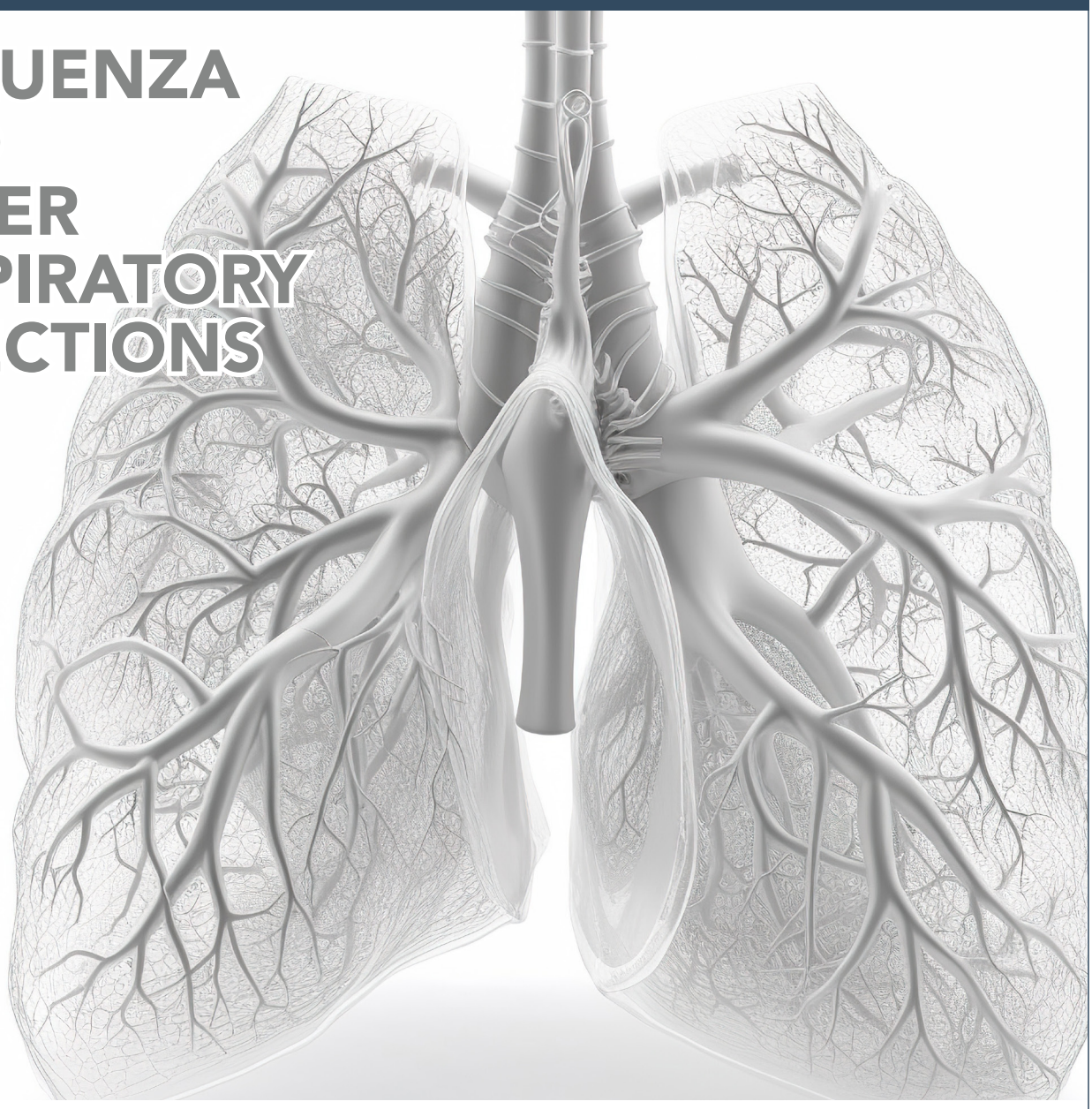
INFLUENZA AND OTHER RESPIRATORY INFECTIONS



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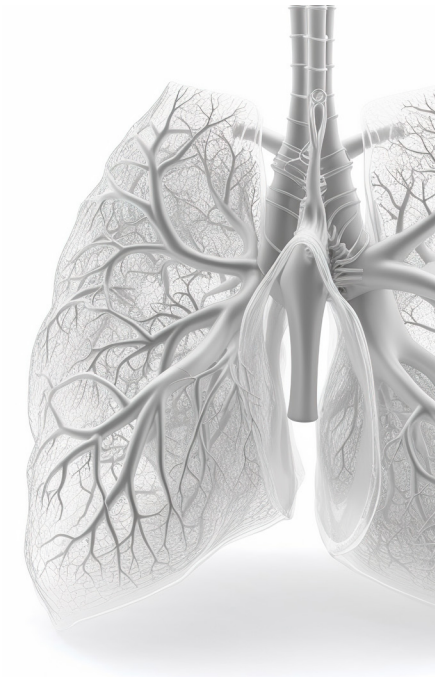

TABLE OF CONTENTS

Summary of the National Advisory Committee on Immunization (NACI) Seasonal Influenza Vaccine Statement for 2023–2024

Angela Sinilaite[1], Winnie Siu[1,2], Jesse Papenburg[3,4,5,6] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: The National Advisory Committee on Immunization (NACI) reviews the evolving evidence on influenza immunization and provides annual recommendations regarding the use of seasonal influenza vaccines. The NACI *Statement on Seasonal Influenza Vaccine for 2023–2024* updates the 2022–2023 NACI recommendations.

Objective: To summarize the 2023–2024 NACI seasonal influenza vaccine recommendations and to highlight new and updated information.

Methods: In the preparation of the *Statement on Seasonal Influenza Vaccine for 2023–2024*, the NACI Influenza Working Group applied the NACI evidence-based process to critically appraise the available evidence and to propose recommendations. The recommendations were then considered and approved by NACI in light of the available evidence.

Results: Key changes for the 2023–2024 season include: 1) incorporation of updated information/guidance on influenza vaccination in the context of the coronavirus disease 2019 (COVID-19); 2) new recommendations for Flucelvax® Quad and Influvac® Tetra, the two quadrivalent inactivated influenza vaccines with expanded paediatric age indications; and 3) an update to the format of the Statement.

Conclusion: Overall, NACI continues to recommend that an age-appropriate influenza vaccine should be offered annually to all individuals aged six months and older who do not have a contraindication to the vaccine, with particular focus on the groups for whom influenza vaccination is particularly recommended.

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Introduction

In Canada, seasonal influenza epidemics generally occur in the late fall and winter months and can lead to significant morbidity and mortality (1). The burden of influenza varies from year to year and some groups, including young children (younger than six years of age), older adults (65 years of age and older), people with chronic health conditions, pregnant individuals and Indigenous peoples are at higher risk of experiencing severe illness, complications or worsening of chronic health conditions. Influenza vaccination is a critical tool to mitigate ongoing health system stress through protection against influenza-related disease.

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with annual recommendations regarding the use of authorized seasonal influenza vaccines, which reflect identified changes in influenza epidemiology, immunization practises and influenza vaccine products available for use in Canada. The annual update of

the NACI statement on seasonal influenza vaccine is led by the NACI Influenza Working Group (IWG) and involves a thorough review and evaluation of the literature as well as discussion and debate at the scientific and clinical practice levels. On May 31, 2023, PHAC released new guidance from NACI on the use of seasonal influenza vaccines for the 2023–2024 season, which is based on current evidence and expert opinion. This article provides a concise summary of NACI's recommendations and supporting information for the 2023–2024 influenza season, including conclusions from evidence reviews on two quadrivalent inactivated influenza vaccines with expanded age indications in children six months of age and older. Updated NACI guidance on concurrent administration of influenza vaccines with the coronavirus disease 2019 (COVID-19) vaccines is also highlighted. Complete details are available in the new NACI Advisory Committee *Statement on Seasonal Influenza Vaccine for 2023–2024* (the Statement) on the PHAC website (2).

Methods

When preparing the *Statement on Seasonal Influenza Vaccine for 2023–2024*, the NACI IWG identified the need for evidence reviews for new topics, reviewed and analyzed the available evidence, and proposed updated recommendations according to the NACI evidence-based process for developing recommendations (3). Further details regarding the strength of NACI recommendations are available in **Table A1** in the **Appendix**. NACI's peer-reviewed framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix) were applied to help ensure that issues related to ethics, equity, feasibility and acceptability are systematically assessed and integrated into NACI guidance (4).

Results

New or updated information for 2023–2024

The 2023–2024 Statement includes updated information and guidance on influenza in the context of COVID-19, including an overview of changes in influenza epidemiology over the course of the COVID-19 pandemic and updated content on concurrent administration of influenza vaccines with COVID-19 vaccines. NACI guidance states that administration of COVID-19 vaccines may occur at the same time as, or at any time before or after, influenza immunization (including all parenteral and intranasal seasonal influenza vaccines) for individuals six months of age and older. Updated NACI guidance and additional information on concurrent administration of COVID-19 vaccines with influenza vaccines and across all eligible age groups is available in the COVID-19 vaccines: Canadian Immunization Guide chapter (5).

For the 2023–2024 influenza season, NACI reviewed the available evidence and developed updated recommendations for:

1) Flucelvax® Quad, a mammalian cell culture-based influenza vaccine (IIV4-cc)

2) Influvac® Tetra, an egg-based, standard dose influenza vaccine (IIV4-SD)

NACI provided the following new recommendations based on a review and analysis of Health Canada assessments of supporting clinical trial evidence submitted by the manufacturers:

1) **NACI recommends that Flucelvax Quad may be considered among the quadrivalent influenza vaccines offered to adults and children six months of age and older (Discretionary NACI Recommendation)**

2) **NACI recommends that Influvac Tetra may be considered among the standard dose inactivated quadrivalent influenza vaccines offered to individuals three years of age and older (Discretionary NACI Recommendation)**

   At this time, NACI concludes that there is insufficient evidence for recommending vaccination with Influvac Tetra in children younger than three years of age (Discretionary NACI Recommendation).

NACI will continue to monitor the evidence as it emerges, and update recommendations as needed. To improve readability and access to information, the format and structure of the Statement has been updated from previous seasons' statements. Notably, clinical information on seasonal influenza vaccine administration for vaccine providers is now contained in the new Influenza vaccines chapter of the Canadian Immunization Guide (6).

Summary of National Advisory Committee on Immunization recommendations for the use of influenza vaccines for the 2023–2024 influenza season

NACI continues to recommend influenza vaccination to anyone six months and older who does not have a contraindication to the vaccine. Vaccination should be offered as a priority to people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk of complications, and others as indicated in **List 1**.

Recommended influenza vaccine options by age group, and recommended dose and route of administration of influenza vaccine types by age, are summarized in **Table 1** and **Table 2** respectively.

List 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization

- All children 6–59 months of age
- Adults and children with the following chronic health conditions[a]:
  - Cardiac or pulmonary disorders (includes bronchopulmonary dysplasia, cystic fibrosis and asthma)
  - Diabetes mellitus and other metabolic diseases
  - Cancer, immune compromising conditions (due to underlying disease, therapy, or both, such as solid organ transplant or hematopoietic stem cell transplant recipients)
  - Renal disease
  - Anemia or hemoglobinopathy
  - Neurologic or neurodevelopment conditions (includes neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders [and, for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions)[b]
  - Morbid obesity (body mass index of 40 kg/m^2 and over)
  - Children six months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza
- All individuals who are pregnant
- People of any age who are residents of nursing homes and other chronic care facilities
- Adults 65 years of age and older
- Indigenous peoples

People capable of transmitting influenza to those at high risk

- Healthcare and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk
- Household contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated:
  - Household contacts of individuals at high risk
  - Household contacts of infants less than six months of age, as these infants are at high risk but cannot receive influenza vaccine
  - Members of a household expecting a newborn during the influenza season
- Those providing regular childcare to children 0–59 months of age, whether in or out of the home
- Those who provide services within closed or relatively closed settings to people at high risk (e.g. crew on a cruise ship)

Others

- People who provide essential community services
- People who are in direct contact with poultry infected with avian influenza during culling operations

[a] Refer to Immunization of Persons with Chronic Diseases and Immunization of Immunocompromised Persons in Part 3 of the CIG for additional information about vaccination of people with chronic diseases (7)
[b] Refer to the NACI *Statement on Seasonal Influenza Vaccine for 2018–2019* (8) for rationale supporting the decision to include persons with neurologic or neurodevelopment conditions among the groups for whom influenza vaccination is particularly recommended and the *Literature Review on Individuals with Neurologic or Neurodevelopment Conditions and Risk of Serious Influenza-Related Complications* (9) for additional details of the evidence reviews that were conducted
Source: List reproduced from NACI *Seasonal Influenza Vaccine Statement for 2023–2024* (2)

Table 1: Recommendations on choice of influenza vaccine type for individual and public health program-level decision making by age group

Recipient by age group	Vaccine types authorized[a,b] for use	Recommendations on choice of influenza vaccine
6–23 months	IIV3-Adj IIV4-SD IIV4-cc	• A quadrivalent influenza vaccine licensed for this age group should be used in infants and young children without contraindications, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine ◦ Currently, there is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age • If a quadrivalent vaccine is not available, a trivalent vaccine licensed for this age group should be used
2–17 years[c]	IIV4-SD IIV4-cc LAIV4	• An age-appropriate quadrivalent influenza vaccine (IIV4-SD, IIV4-cc or LAIV4) should be used in children without contraindications or precautions (see text below applicable to LAIV), including those with chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine ◦ Currently, there is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age • LAIV4 may be given to children with: ◦ Stable, non-severe asthma ◦ Cystic fibrosis who are not being treated with immunosuppressive drugs (e.g. prolonged systemic corticosteroids) ◦ Stable HIV infection, if the child is currently being treated with ART (i.e. HAART) and has adequate immune function • LAIV should not be used in children or adolescents for whom it is contraindicated or for whom there are warnings and precautions such as those with: ◦ Severe asthma (defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing) ◦ Medically attended wheezing in the seven days prior to vaccination ◦ Current receipt of aspirin or aspirin-containing therapy ◦ Immune compromising conditions, with the exception of stable HIV infection (i.e. if the child is treated with HAART for at least 4 months and has adequate immune function) ◦ Pregnancy – In pregnancy, IIV4-SD or IIV4-cc should be used instead
18–59 years	IIV4-SD IIV4-cc RIV4 LAIV4	• Any of the available influenza vaccines authorized for this age group should be used in adults 18–59 years of age without contraindications or precautions, noting the following consideration and exceptions: ◦ There is some evidence that IIV may provide better efficacy than LAIV in healthy adults • LAIV is not recommended for: ◦ Pregnant individuals – In pregnancy, IIV4-SD, IIV4-cc or RIV4 should be used instead ◦ Adults with any of the chronic health conditions identified in List 1, including immune compromising condition ◦ Healthcare workers
60–64 years	IIV4-SD IIV4-cc RIV4	• Any of the available influenza vaccines authorized for this age group should be used in adults 60–64 years of age without contraindications
65 years and older[d]	IIV3-Adj IIV4-SD IIV4-HD IIV4-cc RIV4	**Individual-level decision-making** • IIV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older ◦ Other than a recommendation for using IIV-HD over IIV-SD formulations, NACI has not made comparative individual-level recommendations on the use of the other available vaccines in this age group. In the absence of a specific product, any of the available age-appropriate influenza vaccines should be used **Public health program-level decision-making** • Any of the available influenza vaccines authorized in this age group should be used ◦ There is insufficient evidence on the incremental value of different influenza vaccines (i.e. cost-effectiveness assessments have not been performed by NACI) to make comparative public health program-level recommendations on the use of the available vaccines

Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; IIV, inactivated influenza vaccine; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV4-cc, quadrivalent mammalian cell-culture based inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; NACI, National Advisory Committee on Immunization; RIV4, quadrivalent recombinant influenza vaccine

[a] IIV3-SD formulation will not be authorized or available for use in Canada during the 2023–2024 influenza season

[b] IIV3-HD formulations will not be authorized or available for use in Canada during the 2023–2024 influenza season

[c] Refer to Table 3 of the NACI *Seasonal Influenza Vaccine Statement for 2023–2024* for a summary of vaccine characteristics of LAIV compared with IIV in children 2–17 years of age

[d] Refer to Table 4 of the NACI *Seasonal Influenza Vaccine Statement for 2023–2024* for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older

Source: Table reproduced from NACI *Seasonal Influenza Vaccine Statement for 2023–2024* (2)

Table 2: Recommended dose and route of administration, by age, for influenza vaccine types authorized for the 2023–2024 influenza season

Age group	Influenza vaccine type (route of administration)						Number of doses required
	IIV4-SD[a] (IM)	IIV4-cc[b] (IM)	IIV3-Adj[c] (IM)	IIV4-HD[d] (IM)	RIV4[e] (IM)	LAIV4[f] (intranasal)	
6–23 months	0.5 mL[g]	0.5 mL	0.25 mL	-	-	-	1 or 2[h]
2–8 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1 or 2[h]
9–17 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	0.5 mL	-	-	0.5 mL	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	0.5 mL	-	-	0.5 mL	-	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.7 mL	0.5 mL	-	1

Abbreviations: IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV4-cc, quadrivalent mammalian cell culture based inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; IM, intramuscular; LAIV4, quadrivalent live attenuated influenza vaccine; RIV4, quadrivalent recombinant influenza vaccine

[a] Afluria® Tetra (5 years and older), Flulaval® Tetra (6 months and older), Fluzone® Quadrivalent (6 months and older), Influvac® Tetra (3 years and older)

[b] Flucelvax® Quad (6 months and older)

[c] Fluad Pediatric® (6–23 months) or Fluad® (65 years and older)

[d] Fluzone® High-Dose Quadrivalent (65 years and older)

[e] Supemtek™ (18 years and older)

[f] FluMist® Quadrivalent (2–59 years)

[g] Evidence suggests moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full-vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines (10,11). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to *Statement on Seasonal Influenza Vaccine for 2011–2012* (12)

[h] Children six months to less than nine years of age receiving seasonal influenza vaccine for the first time in their life should be given two doses of influenza vaccine, with a minimum interval of four weeks between doses. Children six months to less than nine years of age who have been properly vaccinated with one or more doses of seasonal influenza vaccine in the past should receive one dose of influenza vaccine per season thereafter

Source: Table reproduced from NACI *Seasonal Influenza Vaccine Statement for 2023–2024* (2)

Conclusion

NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications). Influenza vaccination is particularly important for people at high risk of influenza-related complications or hospitalization; people capable of transmitting influenza to those at high risk; people who provide essential community services; and people in direct contact during culling operations with poultry infected with avian influenza. For the 2023–2024 influenza season, NACI advises that: 1) Flucelvax® Quad may be considered among the quadrivalent influenza vaccines offered to adults and children six months of age and older and 2) Influvac® Tetra may be considered among the standard dose inactivated quadrivalent influenza vaccines offered to individuals three years of age and older.

Authors' statement

AS — Writing, original draft, review, editing
WS — Writing, review, editing
JP — Review, editing

The *NACI Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2023–2024* was prepared by A Sinilaite, A Gil, W Siu and J Papenburg, on behalf of the NACI Influenza Working Group, and was approved by NACI.

Competing interests

J Papenburg reports grants to his institution from MedImmune and Merck and personal fees from AstraZeneca and Merck, all of which were outside of the submitted work.

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Appendix

Table A1: Strength of the National Advisory Committee on Immunization recommendations

Strength of NACI recommendation (based on factors not isolated to strength of evidence, e.g. public health need)	Strong	Discretionary
Wording	"**should/should not** be offered"	"**may be** considered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR known/anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A discretionary recommendation may be considered for some populations/individuals in some circumstances Alternative approaches may be reasonable

Abbreviation: NACI, National Advisory Committee on Immunization

National Influenza Annual Report, Canada, 2022–2023: Canada's first fall epidemic since the 2019–2020 season

Kara Schmidt[1]*, Myriam Ben Moussa[1], Steven Buckrell[1], Abbas Rahal[1], Taeyo Chestley[2], Nathalie Bastien[2], Liza Lee[1]

Abstract

Coinciding with the beginning of the coronavirus disease 2019 (COVID-19) pandemic in March 2020, Canadian seasonal influenza circulation was suppressed, which was a trend reported globally. Canada saw a brief and delayed return of community influenza circulation during the spring of the 2021–2022 influenza season. Surveillance for Canada's 2022–2023 seasonal influenza epidemic began in epidemiological week 35 (week starting August 28, 2022) and ended in epidemiological week 34 (week ending August 26, 2023). The 2022–2023 season marked the return to pre-pandemic-like influenza circulation. The epidemic began in epidemiological week 43 (week ending October 29, 2022) and lasted 10 weeks. Driven by influenza A(H3N2), the epidemic was relatively early, extraordinary in intensity, and short in length. This season, a total of 74,344 laboratory-confirmed influenza detections were reported out of 1,188,962 total laboratory tests. A total of 93% of detections were influenza A (n=68,923). Influenza A(H3N2) accounted for 89% of the subtyped specimens (n=17,638/19,876). Late-season, Canada saw community circulation of influenza B for the first time since the 2019–2020 season. The 2022–2023 influenza season in Canada had an extraordinary impact on children and youth; nearly half (n=6,194/13,729, 45%) of reported influenza A(H3N2) detections were in the paediatric (younger than 19 years) population. Weekly paediatric influenza-associated hospital admissions were persistently above historical peak levels for several weeks. The total number of influenza-associated paediatric hospitalizations (n=1,792) far exceeded historical averages (n=1,091). With the return of seasonal influenza circulation and endemic co-circulation of multiple high burden respiratory viruses, sustained vigilance is warranted. Annual seasonal influenza vaccination is a key public health intervention available to protect Canadians.

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Keywords: influenza, epidemic, surveillance, paediatric, influenza A(H3N2), influenza A(H1N1), influenza B, Canada

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Introduction

Globally, comprehensive nonpharmaceutical interventions (NPIs) implemented in March 2020 aimed at reducing the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), suppressed seasonal influenza epidemic activity into the period of the usual 2021–2022 Northern Hemisphere season (1–8). Canada saw the return of community influenza circulation in the spring of 2022, coinciding with easing of NPIs, which was characterized by a late, low-intensity, and brief seasonal influenza epidemic (9). This 2022–2023 influenza season saw the first re-emergence of pre-pandemic-like influenza circulation patterns in Canada (10).

Suppressed seasonal influenza activity in recent years, and resulting growing population susceptibility, has raised concerns about the timing, impact, and severity of re-emerging post-pandemic seasonal influenza epidemics (3,9,11). Ongoing and timely surveillance plays a critical role in the Public Health Agency of Canada's ability to respond to influenza and other respiratory virus trends, monitor changes in circulation patterns,

and effectively prepare and plan for mitigation measures within the influenza season.

This surveillance report summarizes trends observed during the 2022–2023 influenza season in Canada through analysis of FluWatch core indicators reported by the Public Health Agency of Canada from August 28, 2022 (epidemiological week 35) to August 26, 2023 (epidemiological week 34).

Methods

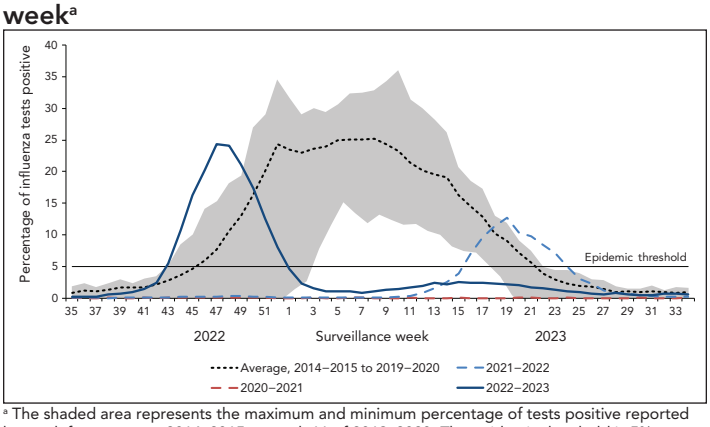
FluWatch is Canada's long-standing influenza surveillance system, which monitors the spread of influenza and influenza-like illness (ILI) through core surveillance indicators based on global epidemiological standards (12). FluWatch is a composite surveillance system that consists of eight key areas: virological surveillance; geographic spread; syndromic surveillance; severe outcome surveillance; outbreak surveillance; influenza strain characterization; vaccination coverage; and vaccine effectiveness (13). Annually, influenza surveillance is conducted across Canada from epidemiological week 35 to week 34 of the following year. For the 2022–2023 Canadian influenza season, this surveillance period began on August 28, 2022, and ended on August 26, 2023. Detailed methods, including surveillance indicator definitions, data sources and statistical analyses, can be found on the Public Health Agency of Canada's FluWatch website (13).

Results

Virological

The 2022–2023 national influenza epidemic began early in the season, exceeding the seasonal epidemic threshold (5% or more positive tests and 15 or more detections) in week 43 (late-October). For the second consecutive season, the Canadian influenza epidemic was brief in duration, lasting only 10 weeks, ending week 1 (early-January; **Figure 1**). Compared to pre-pandemic seasons, this tied the earliest start of an epidemic with the 2018–2019 season. The end of the season was unprecedentedly early, as pre-pandemic epidemics consistently ended around week 22 (late-May).

Figure 1: Percentage of influenza tests positive in Canada compared to previous seasons by surveillance week[a]



[a] The shaded area represents the maximum and minimum percentage of tests positive reported by week from seasons 2014–2015 to week 11 of 2019–2020. The epidemic threshold is 5% tests positive for influenza. When it is exceeded, and a minimum of 15 weekly influenza detections are reported, a seasonal influenza epidemic is declared

During the 2022–2023 Canadian influenza epidemic, influenza activity peaked in week 47 (late-November) at 24.3% tests positive. This was the first time since the declaration of the COVID-19 pandemic that peak activity approached peak levels observed in pre-pandemic seasons (average 31.3%).

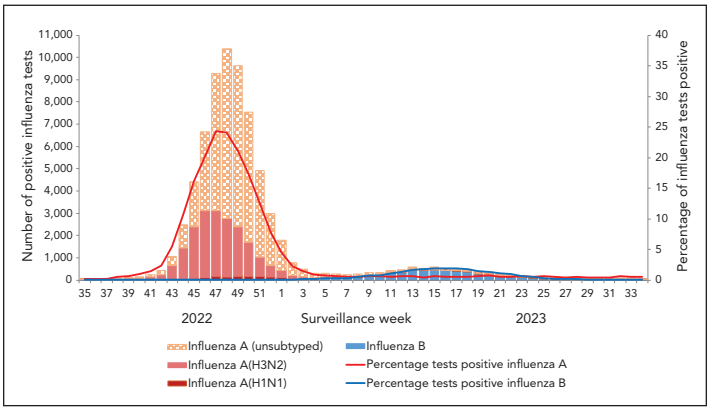
During the 2022–2023 influenza season, a total of 74,344 laboratory-confirmed influenza detections were reported out of 1,188,962 total laboratory tests (**Table 1**). This is both the most detections and most tests ever recorded in a single season, as test counts have increased dramatically from pre-pandemic seasons (average of 276,592 tests and 47,018 detections from seasons 2014–2015 to 2018–2019).

Table 1: Number of laboratory tests, detections, and percentage positivity by influenza season, seasons 2014–2015 to 2022–2023, Canada

Season	Influenza tests	Influenza detections	Cumulative percentage of tests positive	Influenza A detections	Influenza B detections	Total influenza A subtyped	Influenza A(H1N1) detections	Influenza A(H3N2) detections
2014–2015	246,930	42,976	17.4%	34,460 (80%)	8,516 (20%)	13,168	94 (1%)	13,074 (99%)
2015–2016	237,826	39,373	16.6%	28,422 (72%)	10,951 (28%)	12,345	11,168 (90%)	1,177 (10%)
2016–2017	267,827	39,365	14.7%	34,848 (89%)	4,517 (11%)	17,747	179 (1%)	17,568 (99%)
2017–2018	319,916	64,337	20.1%	36,103 (56%)	28,234 (44%)	12,443	1,280 (10%)	11,163 (90%)
2018–2019	310,462	49,037	15.8%	46,497 (95%)	2,540 (5%)	17,374	11,606 (67%)	5,768 (33%)
2019–2020	526,483	55,780	10.6%	32,891 (59%)	22,889 (41%)	7,246	4,985 (69%)	2,261 (31%)
2020–2021	666,576	71	0.0%	48 (68%)	23 (32%)	19	6 (32%)	13 (68%)
2021–2022	751,900	16,126	2.1%	15,894 (99%)	232 (1%)	4,734	83 (2%)	4,651 (98%)
2022–2023	1,188,962	74,344	6.3%	68,923 (93%)	5,421 (7%)	19,876	2,238 (11%)	17,638 (89%)

Influenza A circulated predominantly during the first half of the season and influenza B circulated predominantly in the latter half of the season (**Figure 2**). Overall, a total of 93% of detections were influenza A (n=68,923). Among influenza A subtypes, influenza A(H3N2) predominated, accounting for 89% (n=17,638) of the 19,876 subtyped specimens.

Figure 2: Number of positive influenza tests and percentage of tests positive in Canada, by type, subtype and surveillance week, 2022–2023 influenza season



Detailed information on age and influenza type/subtype was received for 54,096 laboratory-confirmed influenza detections. Influenza A detections were most common among individuals aged 65 years and older (27%; n=13,433), followed by individuals aged 5–19 years (22%; n=11,215). During the 2022–2023 epidemic, the increase in cases in this younger age group preceded increases in all other age groups (**Figure 3**).

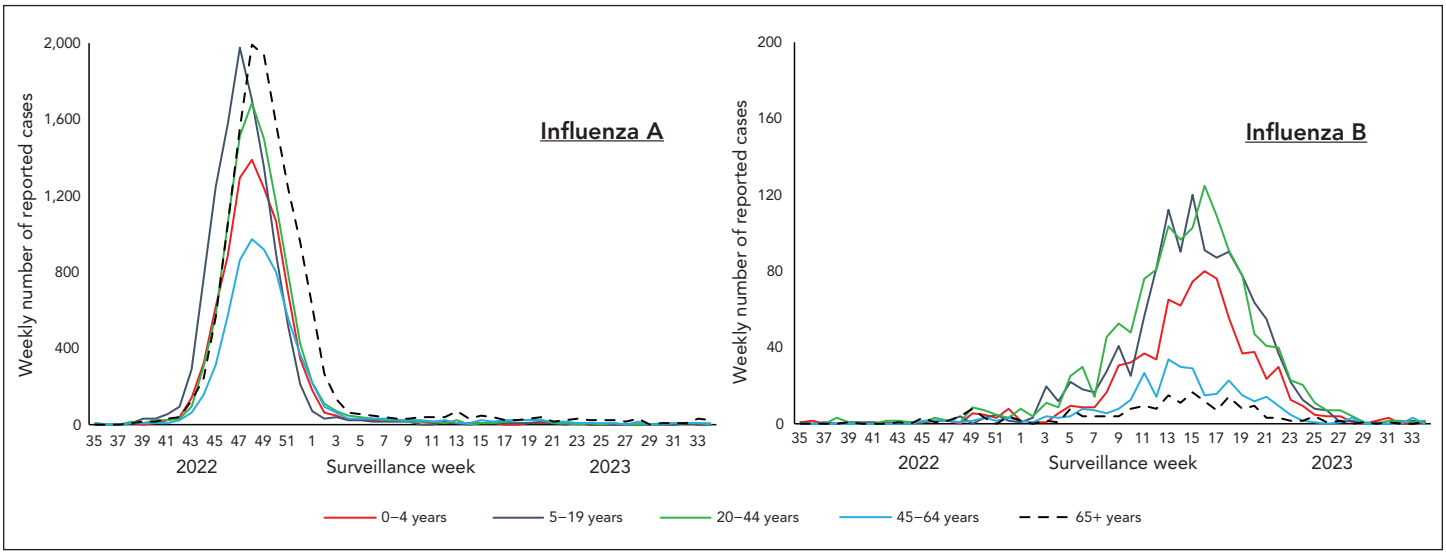
Similar to last season, the age distribution of influenza A(H3N2) cases was much younger than pre-pandemic seasons. Nearly half of influenza A(H3N2) detections (45%) were among individuals aged 0–19 years compared to an average of 17% in pre-pandemic seasons (**Table 2**).

Conversely, influenza B detections were least common among individuals aged 65 years and older (5%; n=196) and 45–64 years (8%; n=327; **Table 3**). A similar case age distribution was observed in pre-pandemic seasons where influenza B Victoria lineage predominated over Yamagata lineage. In each of these seasons, cases occurred least frequently in these older age groups.

Influenza/influenza-like illness activity levels

Sporadic influenza activity was reported by at least 10 reporting regions in each week of the 2022–2023 season. Localized activity was also reported by at least one reporting region in each week of the 2022–2023 influenza season. Coinciding with peak percent positivity observed in FluWatch's virological data, national influenza activity levels peaked between weeks 45 and 52 (early-November to late-December), where widespread activity was reported every week (**Figure 4**). No widespread influenza activity was reported after week 52 (late-December). The sharp decline at weeks 50 and 51 coincided with the holiday season, where data was not reported by many regions.

Figure 3: Count of influenza A (left) and influenza B (right) cases in Canada by surveillance week and age group, 2022–2023 influenza season[a]



[a] The y-axis scale differs across panels

Table 2: Number and percentage of seasonal influenza A(H3N2) detections by influenza season, by age group, seasons 2014–2015 to 2022–2023, Canada

Age group (years)	Influenza season[a]															
	2014–2015		2015–2016		2016–2017		2017–2018		2018–2019		2019–2020[b]		2021–2022		2022–2023	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0–4	813	6%	79	7%	835	7%	682	7%	275	5%	214	10%	574	19%	2,730	20%
5–19	970	8%	104	10%	1,080	10%	710	7%	506	10%	264	12%	805	27%	3,464	25%
20–44	1,697	14%	175	17%	1,810	16%	1,388	14%	660	13%	344	16%	805	27%	2,647	19%
45–64	1,687	13%	214	20%	1,983	18%	1,595	16%	724	14%	316	15%	293	10%	1,556	11%
65+	7,365	59%	485	46%	5,462	49%	5,882	57%	2,957	58%	981	46%	514	17%	3,332	24%
Total	12,532	N/A	1,057	N/A	11,170	N/A	10,257	N/A	5,122	N/A	2,148	N/A	2,991	N/A	13,729	N/A

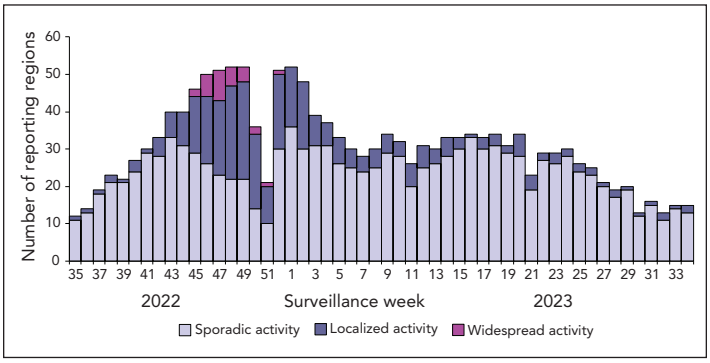
Abbreviation: N/A, not applicable
[a] The 2020–2021 season was excluded from Table 2 as <5 total influenza A(H3N2) cases with age information were reported
[b] During the 2019–2020 season, case data from one jurisdiction used 20–64-year age group instead of 20–44 and 45–64. These cases have been omitted from the age group-specific case counts but are included in the total case counts

Table 3: Number and percentage of seasonal influenza B detections by influenza season, by age group, seasons 2014–2015 to 2022–2023, Canada

Age group (years)	Influenza season (predominant influenza B lineage)[a,b]															
	2014–2015 Yamagata		2015–2016 Victoria		2016–2017 Yamagata		2017–2018 Yamagata		2018–2019 Victoria		2019–2020 Victoria[c]		2021–2022 N/A[d]		2022–2023 Victoria	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0–4	569	8%	1,800	19%	293	9%	1,615	7%	379	20%	4,170	22%	43	22%	807	21%
5–19	810	11%	2,765	29%	549	17%	2,994	13%	638	34%	6,094	32%	28	14%	1,233	31%
20–44	1,157	16%	2,262	24%	536	17%	3,051	13%	434	23%	5,737	30%	46	24%	1,361	35%
45–64	1,850	25%	1,150	12%	737	23%	5,098	21%	144	8%	1,203	6%	27	14%	327	8%
65+	2,935	40%	1,640	17%	1,053	33%	11,015	46%	276	15%	1,455	8%	51	26%	196	5%
Total	7,321	N/A	9,617	N/A	3,168	N/A	23,773	N/A	1,871	N/A	18,878	N/A	195	N/A	3,924	N/A

Abbreviation: N/A, not applicable
[a] The 2020–2021 season was excluded from Table 3 as <5 total influenza B cases with age information were reported
[b] Predominant lineage was determined by influenza B specimen antigenic characterization performed by the National Microbiology Laboratory. In each season, >75% of characterized specimens belonged to either Victoria or Yamagata lineage with predominance attributed to the lineage exceeding this threshold
[c] During the 2019–2020 season, case data from one jurisdiction used 20–64 years age group instead of 20–44 and 45–64. These cases have been omitted from the age group-specific case counts but are included in the total case counts
[d] There were no influenza B specimens received and characterized by the National Microbiology Laboratory during the 2021–2022 season, therefore no predominant lineage could be assigned

Figure 4: Number of influenza surveillance regions reporting sporadic, localized, or widespread activity by surveillance week in Canada, 2022–2023 influenza season

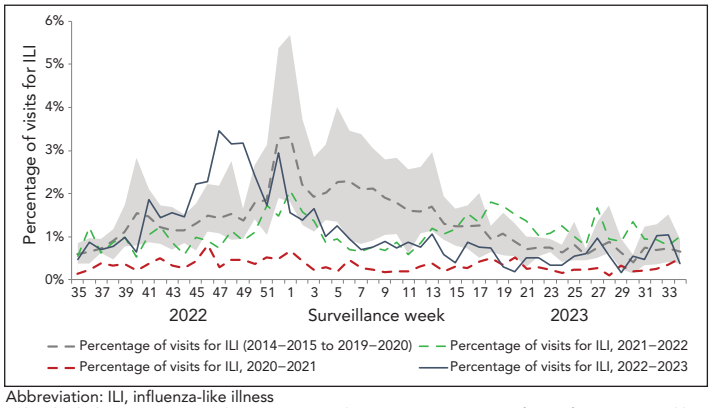


Syndromic-sentinel primary healthcare provider influenza-like illness surveillance

During the 2022–2023 influenza season, a weekly average of 3,144 patients were seen by a weekly average of 42 sentinel primary care providers. Both metrics were lower than the 2021–2022 season, where an average of 50 sentinel primary care providers saw a weekly average of 3,769 patients.

During that season, the weekly percentage of visits to primary care providers for ILI followed expected trends, ranging between 0.2% and 3.5% (**Figure 5**). The percentage of weekly visits for ILI remained within historical levels until week 45 (early-November), peaked in week 47 (late-November) at 3.5%, and remained above historical levels until week 51 (late-December). Influenza-like illness visits remained within or below historical levels for the remainder of the 2022–2023 season. Influenza-like illness visit trends coincided with increases in influenza activity and ultimately reflected the timing of the 2022–2023 influenza season.

Figure 5: Percentage of visits for influenza-like illness reported by sentinel primary care providers in Canada by season and surveillance week[a]

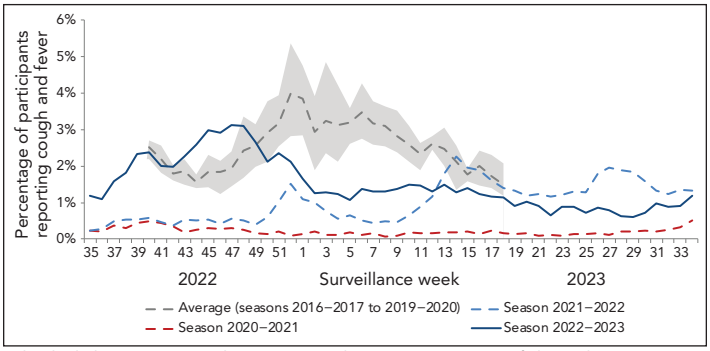


Abbreviation: ILI, influenza-like illness
[a] The shaded area represents the maximum and minimum percentage of visits for ILI reported by week from seasons 2014–2015 to week 11 of 2019–2020

Syndromic-FluWatchers

During the 2022–2023 season, an average of 10,142 FluWatchers reported each week, with a total of 15,755 FluWatchers participating over the season and a total of 527,363 questionnaires submitted. The percentage of FluWatchers reporting ILI symptoms (acute onset of cough and fever) surpassed historical levels in week 42 (mid-October), peaked in week 47 (late-November) at 3.1%, and remained above historical levels until week 48 (early-December; **Figure 6**). Levels gradually decreased and remained below expected levels until the end of the 2022–2023 season. Self-reported ILI did not increase significantly over the period of influenza B circulation.

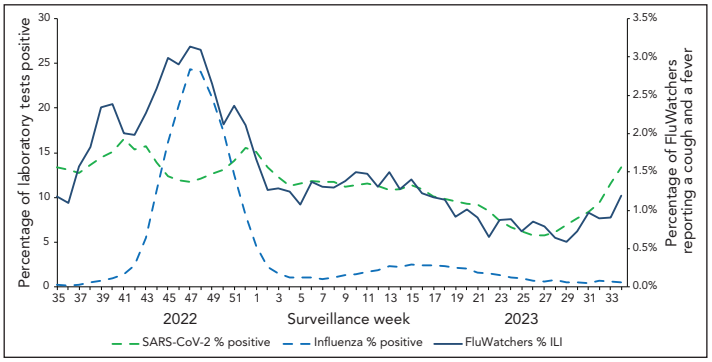
Figure 6: Percentage of FluWatcher participants reporting cough and fever in Canada by season and surveillance week[a]



[a] The shaded area represents the maximum and minimum percentage of FluWatcher participants reporting influenza-like illness by week from seasons 2016–2017 to week 11 of 2019–2020

The reports of ILI are not specific to any one respiratory pathogen and can be due to influenza or other respiratory viruses, including SARS-CoV-2. This makes the proportion of FluWatchers reporting ILI an important indicator of overall respiratory illness activity in the community. The percentage of FluWatchers reporting ILI captured trends in laboratory-confirmed respiratory virus detections, notably of SARS-CoV-2 and influenza. Increases in self-reported ILI tend to mirror increases in both SARS-CoV-2 percent positivity as well as influenza percent positivity (**Figure 7**).

Figure 7: Percentage of influenza and SARS-CoV-2 laboratory tests positive and percentage of FluWatchers reporting cough and fever in Canada by surveillance week, 2022–2023 influenza season



Abbreviations: ILI, influenza-like illness; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Outbreaks

During the 2022–2023 season, 626 laboratory-confirmed influenza outbreaks were reported, with the majority occurring in long-term care facilities (LTCFs) (53.5%), followed by facilities categorized as "other" (28.6%); **Table 4**). The number and proportion (n=335, 53.5%) of laboratory-confirmed influenza outbreaks occurring in LCTFs was lower than recent pre-pandemic seasons (n=639, 62% in 2018–2019; n=615, 64% in 2019–2020). This may be related to differences in reporting among provinces and territories compared to previous seasons. The number of laboratory-confirmed outbreaks reported in a week peaked in week 49 (early-December; n=84), which coincided with the peak of the influenza season.

Severe outcomes-provincial/territorial severe outcome surveillance

During the 2022–2023 season, 4,216 influenza-associated hospitalizations were reported by participating provinces and territories. Most hospitalizations were associated with influenza A (97%), and among hospitalizations with subtype information, 85% (n=1,804) were associated with influenza A(H3N2).

The annual seasonal hospitalization incidence for the 2022–2023 season was 49 hospitalizations per 100,000 population, which is within values recorded in previous seasons (**Table 5**). Among hospitalizations, heterogeneity existed between age groups. The highest cumulative hospitalization rates were among children aged 0–4 years (131 per 100,000 population) and adults aged 65 years and older (131 per 100,000 population). These rates significantly exceeded both the cumulative rates among remaining age groups, a trend observed in last

Table 4: Number and percentage of laboratory-confirmed influenza outbreaks in Canada by setting and season, seasons 2018–2019 to 2020–2023

Year	Long-term care facilities		Acute care facilities		Schools and daycares		Remote or isolated communities		Other	
	n	%	n	%	n	%	n	%	n	%
2018–2019	639	61.6	138	13.3	32	3.1	N/A	N/A	229	22.1
2019–2020	615	64.2	89	9.3	15	1.6	0	0	239	24.9
2020–2021	0	0	0	0	0	0	0	0	0	0
2021–2022	45	51.1	5	5.7	1	1.1	3	3.4	34	38.6
2022–2023	335	53.5	101	16.1	4	0.6	7	1.1	179	28.6

Abbreviation: N/A, not applicable

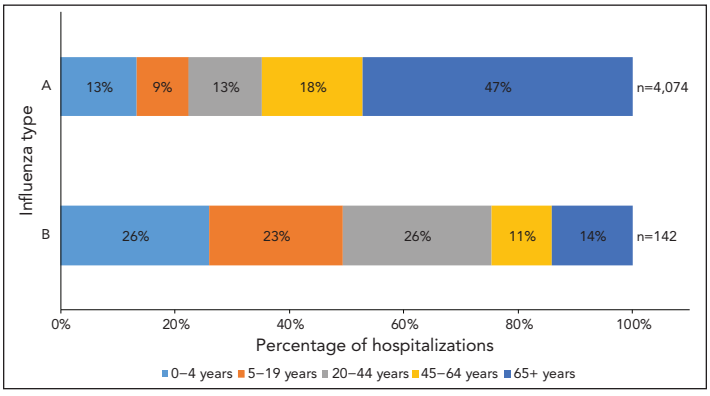
Table 5: Estimated annual seasonal incidence of influenza hospitalizations, per 100,000 population, in Canada by season and age group, seasons 2014–2015 to 2022–2023[a]

Age group (years)	Influenza season (predominant influenza A subtype)							
	2014–2015 (H3N2)	2015–2016 (H1N1)	2016–2017 (H3N2)	2017–2018 (H3N2)	2018–2019 (H1N1)	2019–2020 (H1N1)	2021–2022 (H3N2)	2022–2023 (H3N2)
0–4	46	86[b]	46	70	98	77[b]	19	131[b]
5–19	10	14	9	17	21	16	7	27
20–44	6	10	5	12	15	14	5	19
45–64	16	23	15	41	40	23	6	33
65+	175[b]	52	128[b]	280[b]	127[b]	76	21[b]	131[b]
Overall	37	25	30	64	45	30	9	49

[a] The 2020–2021 season was excluded from Table 5 as no influenza hospitalizations were reported
[b] The shaded cells highlight the age group with the highest estimated incidence of influenza hospitalizations for the respective season

season's predominant influenza A(H3N2) epidemic. However, in pre-pandemic seasons of predominant influenza A(H3N2) circulation, hospitalization rates were much higher among adults aged 65 years and older, relative to younger age groups. Influenza A accounted for the vast majority of hospitalizations. When hospitalizations are broken down by type, the paediatric population (19 years and younger) accounted for 49% of hospitalizations associated with influenza B compared to 22% of hospitalizations associated with influenza A (**Figure 8**).

Figure 8: Age distribution of hospitalizations by influenza type in Canada, 2022–2023 influenza season



This season, 362 intensive care unit (ICU) admissions and 275 deaths were reported by participating provinces and territories. Intensive care unit admissions were most common among adults aged 65 years and older (32%) and 45–64 years of age (28%). Deaths were most common among adults aged 65 years and older (76%). The percentage of hospitalizations that resulted in ICU admissions was comparable to values reported in historical seasons (**Table 6**).

Severe outcomes—Canadian Immunization Monitoring Program, ACTive

The Canadian Immunization Monitoring Program, ACTive (IMPACT) network preliminarily reported 1,792 influenza-associated paediatric hospitalizations during the 2022–2023 influenza season, which was greater than historical seasons. From 2014–2015 to 2019–2020, an average of 1,091 paediatric hospitalizations were reported, with 1,354 hospitalizations being the highest reported in a single season (2018–2019).

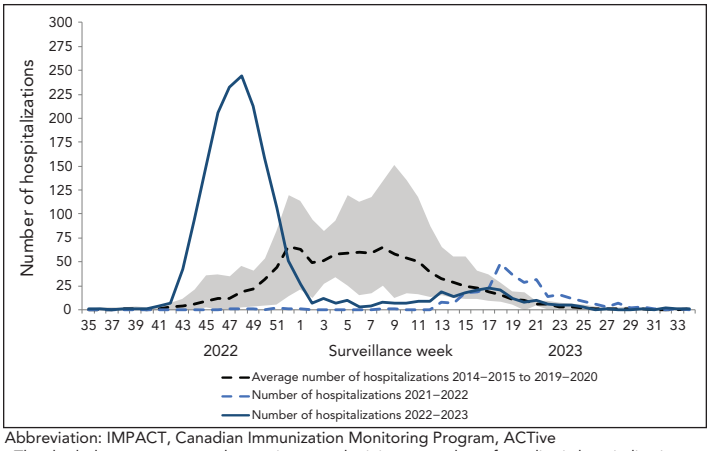
Weekly preliminary paediatric hospitalizations rapidly increased as of week 42 (mid-October) before reaching a peak in week 48 (early-December; n=242; **Figure 9**). This peak was early and of extraordinary intensity. Pre-pandemic (seasons 2014–2015 to 2019–2020), paediatric hospitalizations peaked no earlier than at week 52, at an average of 66 hospitalizations.

Table 6: Percentage of hospitalizations that resulted in intensive care unit admissions in Canada by season and age group, seasons 2014–2015 to 2022–2023[a]

Age group (years)	Influenza season							
	2014–2015	2015–2016	2016–2017	2017–2018	2018–2019	2019–2020	2021–2022	2022–2023
0–4	4%	5%	4%	13%	12%	10%	10%	9%
5–19	6%	6%	6%	18%	13%	14%	6%	7%
20–44	9%	14%	8%	14%	22%	10%	11%	11%
45–64	10%	17%	9%	19%	28%	20%	13%	14%
65+	4%	7%	3%	7%	12%	10%	7%	6%
Overall	5%	10%	4%	10%	17%	12%	9%	9%

[a] The 2020–2021 season was excluded from Table 6 as no influenza hospitalizations were reported

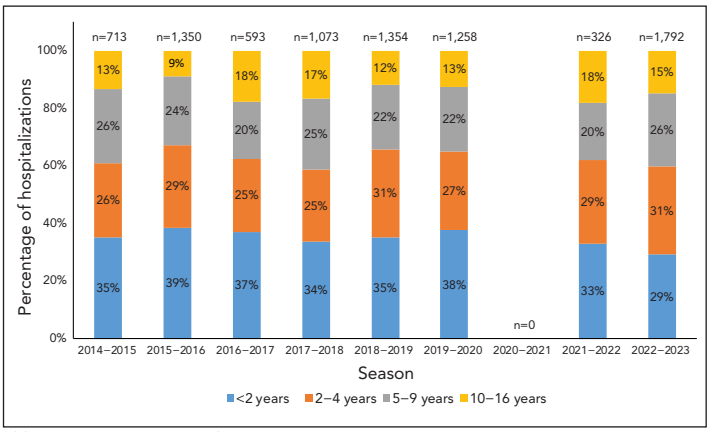
Figure 9: Preliminary weekly number of paediatric hospitalizations in Canada, reported by IMPACT by season and week of admission[a]



Abbreviation: IMPACT, Canadian Immunization Monitoring Program, ACTive

[a] The shaded area represents the maximum and minimum number of paediatric hospitalizations reported by IMPACT, by week from seasons 2014–2015 to week 11 of 2019–2020

Figure 10: Age distribution of paediatric hospitalizations in Canada reported by IMPACT, seasons 2014–2015 to 2022–2023



Abbreviation: IMPACT, Canadian Immunization Monitoring Program, ACTive

Most hospitalizations (n=1,612, 90%) were associated with influenza A. Among hospitalizations for which influenza subtype was available, 94% (n=643) were associated with influenza A(H3N2). The overall age distribution of paediatric hospitalizations was not vastly different compared to previous seasons (**Figure 10**). However, for the first time over the last seven influenza epidemics, the proportion of hospitalized cases aged 2–4 years was highest, rather than their younger cohort younger than 2 years of age. The total number and the age distribution of paediatric influenza B-associated hospitalizations were within ranges seen in pre-pandemic seasons (**Table 7**).

This season, 283 ICU admissions and 10 deaths were reported. The highest proportion of ICU admissions was reported among cases aged 2–4 years (29%) and 10–16 years (22%). The percentage of paediatric hospitalizations that resulted in ICU admissions was comparable to values reported in historical seasons (**Table 8**).

Table 7: Number and percentage of paediatric influenza B-associated hospitalizations in Canada reported by IMPACT by age group, seasons 2014–2015 to 2022–2023[a]

Age group (years)	Influenza season													
	2014–2015		2015–2016		2016–2017		2017–2018		2018–2019		2019–2020		2022–2023	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<2	60	30%	138	30%	31	24%	101	25%	32	25%	199	33%	50	28%
2–4	53	26%	118	26%	32	25%	92	23%	44	35%	161	26%	51	28%
5–9	54	27%	145	31%	39	30%	127	31%	34	27%	162	27%	58	32%
10–16	35	17%	60	13%	28	22%	84	21%	17	13%	89	15%	21	12%
Total	202	100%	461	100%	130	100%	404	100%	127	100%	611	100%	180	100%

Abbreviation: IMPACT, Canadian Immunization Monitoring Program, ACTive

[a] The 2020–2021 and 2021–2022 seasons were excluded from Table 7 comparison as no influenza hospitalizations and <5 influenza hospitalizations were reported, respectively

Table 8: Percentage of paediatric hospitalizations that resulted in intensive care unit admissions in Canada reported by IMPACT by age group, seasons 2014–2015 to 2022–2023[a]

Age group (years)	Influenza season							
	2014–2015	2015–2016	2016–2017	2017–2018	2018–2019	2019–2020	2021–2022	2022–2023
<2	10%	13%	13%	17%	17%	16%	8%	16%
2–4	20%	17%	12%	16%	20%	19%	10%	15%
5–9	14%	19%	19%	20%	24%	18%	9%	12%
10–16	22%	29%	29%	26%	24%	25%	19%	23%
Overall	15%	17%	17%	19%	20%	18%	11%	16%

Abbreviation: IMPACT, Canadian Immunization Monitoring Program, ACTive
[a] The 2020–2021 season was excluded from Table 8 as no influenza hospitalizations were reported

Influenza strain characterization

From September 1, 2022, to August 31, 2023, the National Microbiology Laboratory characterized 684 influenza viruses (460 A(H3N2), 108 A(H1N1) and 116 influenza B) that were received from Canadian laboratories.

Genetic characterization influenza A(H3N2)

Ten influenza A(H3N2) viruses did not grow to sufficient hemagglutination titers for antigenic characterization by hemagglutination inhibition (HI) assays. Therefore, the National Microbiology Laboratory performed genetic characterization to determine the genetic group identity of these viruses. Sequence analysis of the hemagglutinin (HA) genes of the viruses showed that they belonged to genetic group 3C.2a1b.2a2. The A/Darwin/6/2021 (H3N2)-like virus is an influenza A(H3N2) component of the 2022–2023 Northern Hemisphere influenza vaccine and belongs to genetic group 3C.2a1b.2a2.

Antigenic characterization

Influenza A(H3N2)

Of the 450 influenza A(H3N2) viruses characterized, 441 were characterized as antigenically similar to A/Darwin/6/2021 (H3N2)-like virus with antisera raised against cell-grown A/Darwin/6/2021 (H3N2)-like virus. Nine viruses showed reduced titer with antisera raised against cell-grown A/Darwin/6/2021 (H3N2)-like virus. The A/Darwin/6/2021 (H3N2)-like virus is an influenza A(H3N2) component of the 2022–2023 Northern Hemisphere influenza vaccine. The 450 influenza A(H3N2) viruses characterized belonged to genetic group 3C.2a1b.2a2.

Influenza A(H1N1)

The 108 influenza A(H1N1) viruses were characterized as antigenically similar to A/Wisconsin/588/2019-like with ferret antisera produced against cell-propagated A/Wisconsin/588/2019. The A/Wisconsin/588/2019 is the influenza A(H1N1) component of the 2022–2023 Northern Hemisphere influenza vaccine.

Influenza B

Influenza B viruses can be divided into two antigenically distinct lineages represented by B/Yamagata/16/88 and B/Victoria/2/87 viruses. The recommended influenza B components for the 2022–2023 Northern Hemisphere influenza vaccine are B/Austria/1359417/2021 (Victoria lineage) and B/Phuket/3073/2013 (Yamagata lineage). The 116 viruses characterized were antigenically similar to B/Austria/1359417/2021.

Antiviral resistance

The 604 influenza viruses (383 A(H3N2), 106 A(H1N1) and 115 influenza B) were tested for antiviral resistance, with 100% of viruses sensitive to oseltamivir and zanamivir.

Vaccination coverage

Influenza vaccination coverage among all adults for the 2022–2023 influenza season (43%) was slightly higher than the previous season (39%). Among those at higher risk of complications from influenza (adults aged 65 years and older and adults aged 18–64 years with chronic medical conditions), vaccination coverage was 74% and 43% respectively, both similar to the previous season and below Canada's influenza vaccination coverage goal of 80% for those at higher risk (14).

Vaccine effectiveness

The Canadian Sentinel Practitioner Surveillance Network provides estimates of the effectiveness of the seasonal influenza vaccine in preventing medically attended illness due to laboratory-confirmed influenza among Canadians (15). Based on data collected between November 1, 2022, and January 6, 2023, vaccine effectiveness was estimated to be 54% against influenza A(H3N2). Due to the dominant circulation of influenza A(H3N2) this season, the vaccine effectiveness estimate was only available for one influenza subtype. By age group, vaccine effectiveness was 47% (95% CI: 11–69) for individuals under the age of 19 years, 58% (95% CI: 33–73) for adults aged 20–64 years and 59% (95% CI: 15–80) for adults aged 65 years and older.

Discussion

The 2022–2023 influenza epidemic in Canada, driven by influenza A(H3N2), was early, intense, and had an extraordinary impact on children and adolescents (10). The national influenza epidemic began in week 43 (late-October), peaked rapidly in week 47 (late-November), and ended unprecedentedly early in week 1 (early-January). Early and intense activity with influenza A(H3N2) predominance was also seen in the United States and Europe this season and in regions of the Southern Hemisphere during their 2022 influenza season (16–19). The intensity of this season's influenza epidemic coincided with unusually early respiratory syncytial virus (RSV) activity and ongoing SARS-CoV-2 circulation, which posed a threat to public health and increased pressures on the Canadian healthcare system.

The dominance of influenza A(H3N2) seen during the 2021–2022 Canadian influenza season continued into the 2022–2023 season. Similar to last season, several FluWatch indicators demonstrated that the paediatric population was atypically afflicted. For the second straight season, nearly half of influenza A(H3N2) cases were aged 0–19 years, more than double the average recorded in pre-pandemic years. Additionally, hospitalization rates were once again similar among children aged 0–4 years and adults aged 65 years and older, a distribution not observed during pre-pandemic influenza A(H3N2) predominant epidemics, where burden is typically highest in older adults. Perhaps most notable, the total number of influenza-associated paediatric hospitalizations preliminarily reported by IMPACT during the 2022–2023 influenza season greatly exceeded the total reported in any pre-pandemic season. Weekly paediatric influenza-associated hospitalization admissions were persistently higher than historical peak levels for several weeks during the 2022–2023 season. As was previously hypothesized, the atypical age distribution may reflect immunologic factors (9,10). A large, unexposed cohort of young children may have been more vulnerable to infection following the suppression of seasonal respiratory virus transmission across Canada in recent years. The percentage of hospitalizations in both paediatrics and adults that resulted in ICU admissions was within values previously reported, suggesting that despite the high number of hospitalizations this season, they were not necessarily more severe.

As the 2022–2023 influenza epidemic waned, so did the dominance of influenza A(H3N2), as increased detections of influenza A(H1N1) and influenza B were observed, which was a trend also seen in other Northern Hemisphere regions (17,20). The small wave of influenza B that occurred later in the season mirrored pre-pandemic patterns with its timing. The National Microbiology Laboratory characterized and classified all influenza B viruses as belonging to B/Victoria lineage. As of February 2023, it was reported by the World Health Organization that there had been no confirmed detections of circulating B/Yamagata lineage viruses since before April 2020 (21).

Historically, in Canada, the age distribution of influenza B cases has differed between influenza B/Victoria and influenza B/Yamagata predominant seasons. In pre-pandemic seasons, where influenza B/Victoria predominated, the majority of influenza B cases were younger than 45 years of age, while the opposite was true of influenza B/Yamagata predominant seasons. This trend has been reported elsewhere and was notable through the 2022–2023 influenza season in Canada, with 87% of influenza B cases younger than 45 years of age (22–25). If influenza B/Yamagata community circulation does not return, there may be future implications for how populations are affected by influenza B.

Canada has not observed widespread circulation of influenza A(H1N1) since the 2019–2020 season, leaving a large unexposed cohort of the general population, especially new cohorts of children younger than four years. The 2023 summer saw waning dominance of influenza A(H3N2) globally, and a resurgence of influenza A(H1N1) activity in the upcoming season is possible. However, an abundance of factors can influence influenza activity and severity: antigenic drift, co-circulation of other respiratory viruses, vaccination coverage, vaccine effectiveness, antiviral use, population imprinting, cohort effects, and contextual factors (25–33).

Though the younger cohort was unusually impacted during the past two influenza epidemics in Canada (9,10), adults with chronic health conditions and older adults remain at high risk of severe outcomes. With endemic co-circulation of multiple high burden respiratory viruses impacting all age groups (influenza, SARS-CoV-2, RSV), and potential emergence of non-seasonal respiratory viruses, the importance of respiratory virus surveillance in Canada is highlighted. Predicting influenza activity is notoriously difficult, and this can be mitigated with comprehensive surveillance activities and the use of historical data and trends to determine likely outcomes to in-season observations. Sustained vigilance and integrated planning approaches for upcoming predictably unpredictable respiratory virus seasons, in the context of a strained healthcare system, are essential (3,29).

Influenza can cause severe illness across all age groups, with or without chronic health conditions (25). Certain populations, such as young children, older adults, individuals with chronic health conditions, residents of LTCF and chronic care facilities, pregnant individuals, and Indigenous peoples are at greater risk of serious complications or worsening of underlying health conditions (34). Annual influenza vaccination remains a critical tool for the prevention of influenza and its complications, and reduced transmissibility to others.

Authors' statement

The FluWatch team in the Public Health Agency of Canada's Centre for Emerging and Respiratory Infections and Pandemic Preparedness developed the first draft of this report collaboratively; all authors contributed to the conceptualization, writing, and revision of the manuscript.

Competing interests

None.

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OVERVIEW

Healthcare costs and effects of post-COVID-19 condition in Canada

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Abstract

Background: As evidence of the long-term health impacts of coronavirus disease 2019 (COVID-19) continues to grow across Canada, a key concern is the costs and health impacts of post-COVID-19 condition (PCC), especially while the healthcare system remains under substantial strain. The objective of this study is to estimate healthcare costs and quality-adjusted life year (QALY) decrements per PCC case and per acute COVID-19 case by vaccination status.

Methods: First, we conducted a rapid review of the literature to estimate 1) the probability of developing PCC following COVID-19 infection by vaccination status, 2) the probability of each condition commonly associated with PCC, 3) healthcare costs and QALY decrements associated with each condition and 4) the number of PCC cases currently in Canada. Second, using the data gathered from the literature, we built a tool to estimate the cost and QALY decrements per PCC and COVID-19 case.

Results: Post-COVID-19 condition costs per COVID-19 case ranged from CAD 1,675 to CAD 7,340, and QALY decrements ranged between 0.047 to 0.206, in the first year following COVID-19 infection. Overall, individuals who were unvaccinated when they were infected had higher costs and QALY decrements. We estimated the total burden of PCC to the Canadian healthcare system based on PCC estimates up until spring 2023 would be between CAD 7.8 and CAD 50.6 billion.

Conclusion: This article demonstrates the large potential health and economic burden of PCC for Canadians, and the importance of vaccination and other infection control strategies in reducing the longer-term costs and effects.

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Keywords: post-COVID condition, economic burden, healthcare costs, costing analysis, quality-adjusted life years, COVID-19

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Introduction

Concerns continue to grow about the long-term impacts of the coronavirus disease 2019 (COVID-19) pandemic. Post-COVID-19 condition (PCC) is often characterized by ongoing symptoms (12 weeks or longer) after the acute phase of COVID-19 infection (1). Symptoms commonly associated with PCC include fatigue, respiratory symptoms, adverse cardiovascular events, psychiatric and cognitive issues, along with other symptoms that impact everyday functioning. Post-COVID-19 condition symptoms can fluctuate over time and include those that persist over many months following acute COVID-19 or brand new symptoms that occur following initial recovery (2). A large retrospective matched cohort study examined risk factors for PCC in adults with confirmed COVID-19 who were propensity score matched to controls without COVID-19 (3). Among the cohort with confirmed COVID-19 infection, risk factors significantly associated with PCC included female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity and a wide range of comorbidities; raising concerns about equity, as impacts of PCC differ among groups of the population.

Many studies have demonstrated a high prevalence of PCC, although the risk of PCC following COVID-19 diagnosis varies widely across studies (5%–80%) (4). Two systematic reviews (5,6)

estimated that 63% to 84% of people with confirmed COVID-19 had symptoms four weeks after either diagnosis or hospitalization and 46% to 56% experienced symptoms after 12 weeks. However, it appears that prevalence decreases with time (i.e. fewer people report symptoms at six to nine months compared to at three months), which may indicate that some people with PCC could recover over time. Studies also suggest those with a higher severity of acute infection (e.g. those hospitalized) may be at a higher risk of PCC compared to people who had milder acute illness (7,8). In 2021, in Canada, there were estimated to be 150,000 individuals with PCC, based on a rapid systematic review (9). A Canadian survey of individuals with confirmed or suspected PCC found close to 50% of respondents had symptoms following acute COVID-19 infection for longer than 11 months (10).

Post-COVID-19 condition is associated with increased healthcare utilization, but there is little evidence estimating health system cost and quality of life impacts. A community-based matched cohort study of Ontario adults, both with and without prior polymerase chain reaction-confirmed COVID-19, estimated healthcare utilization 56 days after initial infection (11). Using a composite measurement, which included home care, long-term care, hospitalization, outpatient, and emergency department visits, they found healthcare utilization was 11% higher in individuals that tested positive for COVID-19 compared to those that did not, leading to an additional 1.4 healthcare encounters per person year (11). However, to date, how these additional healthcare encounters may translate into increased healthcare system costs in Canada, in the short and medium term has not been explored. Moreover, with the variety of symptoms associated with PCC, very little is known about how PCC impacts quality of life in Canada. These estimates are important to help evaluate the economic benefits associated with preventing COVID-19 and PCC, as well as treatments for PCC.

The overall objective of this study is to provide cost and health-related quality of life estimates on PCC and specifically to estimate 1) healthcare costs associated with a PCC case and the cost of PCC per acute COVID-19 case as well as total healthcare cost burden of PCC and 2) quality-adjusted life year (QALY) decrement per PCC case and QALY decrement due to PCC per acute COVID-19 case.

Methods

This analysis built on work by Mulberry *et al.* (12) that estimated the healthcare cost associated with PCC as part of a larger economic evaluation of vaccine roll-out strategies. We updated this analysis to produce estimates of the healthcare cost and QALY decrements associated with PCC per COVID-19 case disaggregated by vaccination status.

In the first step, we conducted a rapid review to 1) estimate the probability of developing PCC following COVID-19 infection and by vaccination status, 2) estimate the number of PCC cases currently in Canada, 3) identify the symptom classes and conditions most commonly associated with PCC, and the probability they will develop, and 4) determine the healthcare costs and QALYs associated with each of the PCC symptom classes.

We conducted the rapid literature review using the PubMed/MEDLINE and Google Scholar databases. Search terms across the four topics included COVID-19, PCC, probability, incidence, symptoms, cost, QALY and Canada, and derivations of these keywords. For a full list of the keywords see the **Appendix A**, **Table A1**. Our search did not include non-English-language articles.

This review did not include a formal quality appraisal, as the studies we needed to conduct the analysis were very diverse in methods. However, when selecting articles for inclusion in the review we prioritized the PCC symptom class, QALY, and costing studies to be included in the analysis based on four factors: 1) Canadian specific data; 2) sample size; 3) the consistency of the reported condition with reported PCC symptoms, and 4) how recently the data were collected. Based on these prioritization criteria, we used the results from the Canadian COVID-19 Antibody and Health Survey to identify symptom class, as it was a large ongoing survey of the Canadian population and provided information across symptoms for PCC. Moreover, since the first three topic areas were focused on COVID-19, we included only papers published after December 2019 in this part of the review.

In the second step, using the data gathered from the literature, we conducted a costing analysis of the cost per PCC case and PCC-associated cost per COVID-19 case. Input parameters derived from the literature included 1) the total number of patients who experienced at least one PCC symptom in Canada by spring 2023, 2) the likelihood of becoming a PCC case stratified by vaccination status, as well as 3) the probabilities, costs and QALY decrements for each of the most common PCC symptom classes.

We reviewed several symptom classes associated with PCC, including, chronic fatigue, cognitive conditions (e.g. brain fog), diabetes, psychiatric conditions (e.g. depression/anxiety), chronic liver disease, chronic kidney disease, adverse cardiovascular events and respiratory disease. We selected the four most common symptom classes (chronic fatigue, cognitive conditions, psychiatric conditions and respiratory disease) for inclusion in the analysis. Costs were captured in 2022 Canadian dollars (CAD) and effects were measured in QALY decrements. For a full list of input parameters see **Table 1**.

Table 1: Input parameters

Variable	Estimate		Source, year publication (reference)
Symptom classes	Probabilities (%)		
	Non-overlapping	Overlapping	
Chronic fatigue	42.99	72.1	Health Infobase, 2022 (13)
Psychiatric conditions	14.43	24.2	
Cognitive conditions	19.62	32.9	
Respiratory disease	22.96	38.5	
Likelihood of becoming a PCC case (by vaccination status)			
Unvaccinated	41.8	N/A	Azzolini *et al.*, 2022 (14)
1st dose	30.0		
2nd dose	17.4		
3rd dose	16.0		
Health related quality of life decrements			
Chronic fatigue	0.36		Versteegh *et al.*, 2016 (15)
Psychiatric conditions	0.21		Steensma *et al.*, 2016 (16)
Cognitive conditions	0.12		Song *et al.*, 2022 (17)
Respiratory disease	0.37		Van Wilder *et al.*, 2019 (18)
Costs (Canadian dollars)			
Chronic fatigue	12,753		Jason *et al.*, 2008 (19)
Psychiatric conditions	4,123		Chiu *et al.*, 2017 (20)
Cognitive conditions	9,939		Zhu *et al.*, 2013 (21)
Respiratory disease	10,641		Bonafede *et al.*, 2011 (22)
Other variables			
Number of patients with at least one PCC symptom	Low: 0.74 million Medium: 2.02 million High: 2.88 million		Health Infobase, 2023 (23) Health Infobase, 2023 (24) Statistics Canada, 2023 (25)

Abbreviations: N/A, not applicable; PCC, post-COVID-19 condition (COVID-19, coronavirus disease 2019)

We estimated costs and QALY decrements of PCC under two scenarios; 1) non-overlapping symptomology; and 2) overlapping symptomology. In the non-overlapping symptomology scenario, we estimated the healthcare costs and QALY decrements assuming PCC symptoms were mutually exclusive. Therefore, in this calculation, someone diagnosed with PCC would have costs and QALY decrements associated with only one symptom class of PCC (see Equation 1). To calculate the probability of an individual with PCC having a specific symptom class, we took the probability of developing each symptom class from the literature and weighted them to sum to one.

In comparison, in the overlapping symptomology scenario individuals infected with COVID-19 had a certain risk of developing each of the PCC symptom classes, and therefore, could have the costs and QALY decrements associated with more than one symptom class (see Equation 2). In this case, the overall probability of PCC was the raw sum of the probability of having each symptom class PCC diagnosis as derived from the literature. We made this assumption because there is no information available in the literature on joint probability by symptom class, or how this impacts healthcare costs and QALY decrements. For example, this assumes that an individual with PCC that causes chronic fatigue and cognitive conditions will have expected healthcare costs and QALY decrements equal to the sum of the costs and QALY decrements of these two conditions individually multiplied by the probability of each condition. All analyses were conducted using a one-year time horizon; however, the tool allows for longer-term analysis of the costs and effects of PCC. For analyses past one year, we apply an annual discount rate of 1.5% to both costs and QALY decrements, following Canadian guidance (26). The full tool is available to view and download.

Equation 1: Cost and quality-adjusted life year decrements per post-COVID-19 condition case and post-COVID-19 condition-associated cost and quality-adjusted life year decrements per acute COVID-19 case in the non-overlapping scenario.

$$Cost\ per\ PCC\ case = \sum_{s=1}^{S}(p_s^n \times c_S)$$

$$Cost\ of\ PCC\ per\ acute\ COVID\text{-}19\ case\ by\ vaccination\ status = p_{pcc}^v \times \sum_{s=1}^{S}(p_s^n \times c_S)$$

$$QALY\ loss\ per\ PCC\ case = \sum_{s=1}^{S}(p_s^n \times u_S)$$

$$QALY\ loss\ of\ PCC\ per\ acute\ COVID\text{-}19\ case\ by\ vaccination\ status = p_{pcc}^v \times \sum_{s=1}^{S}(p_s^n \times u_S)$$

Equation 2: Cost and quality-adjusted life year decrements per post-COVID-19 condition case and post-COVID-19 condition-associated cost and quality-adjusted life year decrements per acute COVID-19 case in the overlapping scenario.

$$Cost\ per\ PCC\ case = \sum_{s=1}^{S}(p_s^o \times c_S)$$

$$Cost\ of\ PCC\ per\ acute\ COVID\text{-}19\ case\ by\ vaccination\ status = p_{pcc}^v \times \sum_{s=1}^{S}(p_s^o \times c_S)$$

$$QALY\ loss\ per\ PCC\ case = \sum_{s=1}^{S}(p_s^o \times u_S)$$

$$QALY\ loss\ of\ PCC\ per\ acute\ COVID\text{-}19\ case\ by\ vaccination\ status = p_{pcc}^v \times \sum_{s=1}^{S}(p_s^o \times u_S)$$

Where:

p_s^n stands for probabilities of symptom classes under the non-overlapping scenario (i.e. weighted probabilities sum to one)

p_s^o stands for probabilities of symptom classes under the overlapping scenario (i.e. raw sum of probabilities)

c_S stands for costs of symptom classes

u_S stands for utility decrements of symptom classes

p_{pcc}^v stands for probability of becoming a PCC case following acute COVID-19 by vaccination status

s stands for array of all symptom classes, s = 1….S

As we described in Equation 1, we first calculated the cost and QALY decrement per PCC case and then we applied the probability of having PCC by vaccination status to estimate the PCC-associated cost and QALY decrement per acute COVID-19 case under the non-overlapping scenario. For Equation 2, since we assumed PCC symptoms may overlap, we estimated the cost and QALY loss from each PCC case would equal the sum of all symptom probabilities multiplied by the costs and QALYs of those symptoms. We then apply the probability of having PCC by vaccination status, to estimate the PCC-associated cost and QALYS decrement per acute COVID-19 case.

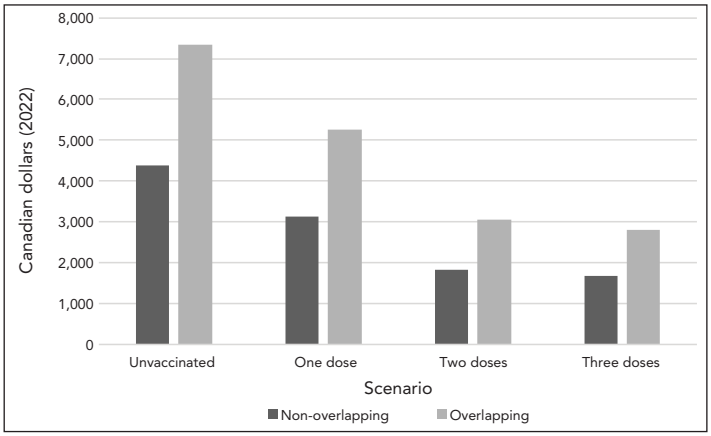
Finally, to estimate total costs associated with PCC in Canada we multiplied the costs per PCC case with the estimated number of PCC cases that have occurred in Canada as of spring 2023. Due to high variability in the literature, we used a range of values for the number of PCC cases. The low estimate was calculated by multiplying confirmed cases of PCC as reported by the Government of Canada as of August 1, 2023 (23), in combination with the lower bound of the confidence interval for the percent of COVID-19 cases that result in PCC (24). The middle value was calculated using 2023 Canadian population estimates (25), in combination with the percent of people reporting testing positive for COVID-19 on rapid antigen or polymerase chain reaction test and the percent of adults reporting PCC following infection (24). Finally, the high value was calculated using the 2023 Canadian population estimates (25), as well as the percent of people either reporting testing positive or having suspected infection, and the high bound of the confidence interval of the percent of cases reporting long-term symptoms (24).

Findings

The results of the non-overlapping symptomology scenario indicate that the costs and QALY decrements per PCC case are CAD 10,471 and 0.29 QALYs within a year, respectively. While the overlapping symptomology scenario indicates higher costs and utility decrements per year associated with PCC, of CAD 17,559 and 0.49, respectively. Based on the estimate on a range of scenarios of the number of Canadians with PCC from CAD 0.74 million to 2.88 million in spring 2023, the total burden to the Canadian healthcare system for one year range between CAD 7.8 and CAD 30.2 billion (middle value: CAD 21.2 billion) in the non-overlapping scenario. Yearly costs of PCC in the overlapping scenario were even higher, ranging from CAD 13.0 to CAD 50.6 billion (middle value: CAD 35.5 billion).

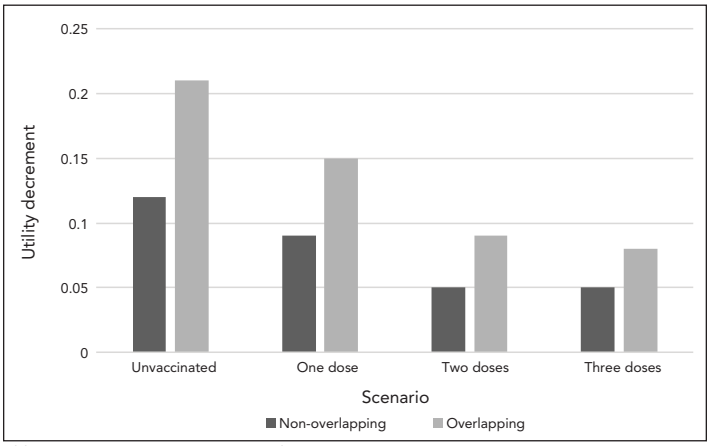
Vaccination had a substantial impact on PCC-associated costs and QALY decrements per acute COVID-19 case calculated under the non-overlapping scenario, presented in **Figure 1** and **Figure 2**. Post-COVID-19 condition cost and QALY decrements per COVID-19 case were 1.4 times, 2.4 times and 2.6 times greater for those who were unvaccinated compared to those vaccinated with one, two and three doses, respectively. **Appendix B** (Scenario analysis findings) provides detailed numeric results for both the overlapping and non-overlapping scenarios.

Figure 1: Annual post-COVID-19 condition cost (in 2022 Canadian dollars) per COVID-19 case by symptomology scenario and vaccination status



Abbreviation: COVID-19, coronavirus disease 2019

Figure 2: Annual post-COVID-19 condition quality-adjusted life years decrement per COVID-19 case by symptomology scenario and vaccination status



Abbreviation: COVID-19, coronavirus disease 2019

Based on the assumption of overlapping symptoms, PCC-associated costs and QALY decrements were at least one and a half times any of the estimates from the non-overlapping scenario. Considering that the majority of the Canadian population has two doses of vaccination (with an expected PCC-associated cost per COVID-19 case of CAD 1,822 in the non-overlapping scenario and CAD 3,055 in the overlapping scenario), we can infer that PCC costs and QALY decrements per acute COVID-19 case in the overlapping scenario are 1.7 times the non-overlapping scenario.

Discussion

We examined the cost and QALY impact of PCC in Canada under two scenarios, both of which emphasize the importance of vaccination. Having at least two doses of COVID-19 vaccine was associated with a large decrease in PCC costs following an acute COVID-19 infection. In comparison, while booster doses still reduced PCC costs and improved QALYs, the marginal benefit was lower. However, as COVID-19 vaccine immunity wanes over time the benefits of booster doses may increase, and it is therefore important to continuously update estimates on the impact of vaccination on PCC.

Both scenarios demonstrate that PCC-associated costs and QALY decrements can be tremendous, ranging from CAD 1,675 to CAD 7,340 per acute COVID-19 case per year. Using current estimates of PCC in Canada, we assessed the healthcare costs associated with these conditions between CAD 7.8 and CAD 50.6 billion per year. Without more information on if and how PCC patients are seeking healthcare, along with PCC severity estimates and recovery times, it is hard to know if the estimates presented here are high or conservative. Therefore, these estimates should be adjusted as more information becomes available in the literature. Alternatively, if individuals with PCC do not seek care for these conditions, or have trouble receiving care, this could manifest in future costs to the healthcare system as conditions worsen. In this analysis we did not capture productivity losses due to PCC, such as absenteeism, presenteeism, or early retirement. Previous research from the United States demonstrates that the productivity losses from PCC may result in economic losses in that country ranging from 101 to USD 403 billion (27).

Limitations

This analysis has several limitations. First, there is a large degree of uncertainty in our results, and these estimates should be updated as more details emerge about the probability of developing PCC, as well as how individuals with PCC seek care and the healthcare costs and QALY decrements associated with the symptoms of PCC. In particular, the nature of the available data meant we needed to make assumptions about the relationship between PCC symptom probabilities, and the costs and outcomes associated with those symptoms, as observed in the differences in the overlapping and non-overlapping estimates. Second, while we searched the literature for the most updated costs and disutility values for the relevant symptom classes, some of the values have not been updated recently, and therefore may not represent current costs and outcomes. However, this tool is easily updated as newer costing and disutility values become available, and there is more information on the risk of PCC and number of Canadians impacted. Third, the literature on development of, and recovery from, PCC is constantly shifting as more data on this population become available. For example, the evidence on recovery from PCC is still developing. This is why we chose to focus on yearly cost estimates, rather than predicting further into the future. Prediction information should be incorporated into this tool as it becomes available to provide accurate information for decision-making. Finally, we provide only a mean-based estimate under two scenarios with ranges around the number of PCC cases in Canada, and future work could take on a more Bayesian approach to the uncertainty in the estimates.

Future directions

The costs and outcomes associated with PCC revealed as part of this analysis also demonstrate the potential for PCC to further strain the Canadian healthcare system. Over the coming years, individuals with PCC will need to access the healthcare system, increasing demand for healthcare labour and other health resources (e.g. diagnostic imaging, pharmaceuticals, PCC treatments). Therefore, future research should explore where PCC is most likely to impact the healthcare system, and where future support may be needed for this population. If they do not receive appropriate care for their long-term symptoms, there could be additional quality of life and return to work impacts; and more research estimating these outcomes is needed in Canada. Moreover, as cases of PCC become increasingly identifiable in health administrative data, future analysis could also take a more direct approach to costing healthcare utilization for those with PCC, including case-control matching, propensity-score matching or micro-costing methods. Finally, the costs and outcomes associated with PCC are unlikely to be evenly felt across the Canadian population, future analysis should focus on subpopulations that may experience disparate and unequal costs and outcomes associated with PCC.

Conclusion

This article demonstrates the large potential health and economic burden of PCC for Canadians and the Canadian healthcare system. Revealing this healthcare cost burden highlights the importance of vaccination and other adequate infection control measures to reduce the long-term healthcare costs. Moreover, the results presented here provides a timely and convenient data source for economic evaluations of COVID-19 prevention programs.

Authors' statement

ER — Conceptualization, data interpretation, writing–review and editing, review and editing of final version
AU — Conceptualization, data acquisition, writing–review and editing, review and editing of final version
EK — Conceptualization, data interpretation, review and editing of final version

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

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Appendix A: Search strategy

We conducted a rapid literature review on PubMed/MEDLINE. We first searched the probability of developing post COVID-19 condition (PCC) following COVID-19 infection. Then, we identified symptoms and conditions most commonly associated with PCC. Once we identified the most common symptoms of PCC, we searched the probabilities, health care costs and quality-adjusted life years (QALYs) associated with each of those symptoms. Finally, we searched the total number of PCC cases currently in Canada. Table A1 presents our search strategy. For the costs and utilities of symptoms, the table reports search terms for only diabetes. A similar strategy was followed for each of the eight symptoms we had identified.

Table A1: Literature search terms

Search concepts	Search terms
Probability of developing PCC following COVID-19 infection	(Probability OR Risk OR Rate OR Likelihood) AND ("Post Covid" OR "Long Covid" OR "Persistent Covid" OR "Post-acute Sequelae of SARS-CoV-2" OR "Long-haul Covid")
Symptoms and conditions most commonly associated with PCC, and the probability they will develop	Symptom* AND ("Post Covid" OR "Long Covid" OR "Persistent Covid" OR "Post-acute Sequelae of SARS-CoV-2" OR "Long-haul Covid")
Probability they will develop	(Prevalence OR Incidence OR Probability OR Rate OR Risk) AND Diabetes AND ("Post Covid" OR "Long Covid" OR "Persistent Covid" OR "Post-acute Sequelae of SARS-CoV-2" OR "Long-haul Covid")
Number of PCC cases currently in Canada	("Prevalence OR Incidence OR Rate OR "Number of" "Total Number") AND ("Post Covid" OR "Long Covid" OR "Persistent Covid" OR "Post-acute Sequelae of SARS-CoV-2" OR "Long-haul Covid") AND Canada
Costs associated with each symptom	Cost* AND Diabetes
QALYs associated with each symptom	(Disutility* OR "Utility Decrement" OR "QALY Decrement" OR "QALY loss") AND Diabetes

Abbreviations: COVID-19, coronavirus disease 2019; PCC, post COVID-19 condition; QALY, quality-adjusted life year; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Appendix B: Scenario analysis findings

Table B1: Overlapping and non-overlapping cost and utility decrements per COVID-19 case

Scenario	Vaccination status	Outcomes
COVID-19 case outcomes non-overlapping scenario		
PCC cost per COVID-19 case (CAD)	Unvaccinated	4,377
	1 dose	3,141
	2 doses	1,822
	3 doses	1,675
PCC QALY decrement per COVID-19 case	Unvaccinated	0.12
	1 dose	0.09
	2 doses	0.05
	3 doses	0.05
COVID-19 case outcomes overlapping scenario		
PCC cost per COVID-19 case (CAD)	Unvaccinated	7,340
	1 dose	5,268
	2 doses	3,055
	3 doses	2,809
PCC QALY decrement per COVID-19 case	Unvaccinated	0.21
	1 dose	0.15
	2 doses	0.09
	3 doses	0.08

Abbreviations: CAD, Canadian; COVID-19, coronavirus disease 2019; PCC, post COVID-19 condition; QALY, quality-adjusted life year

COMMENTARY

Influenza vaccines may protect against cardiovascular diseases: The evidence is mounting and should be known by the Canadian public health community

Philippe De Wals[1,2]*, Michaël Desjardins[3]

Abstract

Evidence on the protective effect of influenza vaccines to prevent cardiovascular disease (CVD) is mounting. We identified 28 systematic reviews/meta-analyses on the effect of influenza vaccines on CVD using different research questions, data sources, selection criteria and outcomes. Most results leaned towards a protective effect. Results of recently published experimental and observational studies not included in these reviews were going in the same direction. The evidence is very robust for cardiovascular deaths and nonfatal myocardial infarction in high-risk individuals, but lower for heart failure, arrhythmia, and stroke and also for all outcomes in low-risk adults. There is also limited evidence for pneumococcal polysaccharide vaccines and evidence has to be collected from ongoing trials on respiratory syncytial virus vaccines. Up to now, this effect has not been considered in economic evaluations of influenza vaccines and its inclusion may change CVD results markedly. This effect is not mentioned in the Canadian Immunization Guide and not known by a majority of vaccinators. The objective of this short commentary is to alert the Canadian public health community and to provide information that could be used at the field level to promote the usefulness of influenza vaccines.

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Keywords: influenza infection, influenza vaccine, cardiovascular disease, pneumonia

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Introduction

Evidence on the protective effect of influenza vaccines to prevent cardiovascular disease (CVD) is mounting. Recognition of this effect could modify results of economic evaluations markedly and also the way they are promoted. Influenza infections in adults are associated with an increased risk of adverse cardiovascular events, including sudden death, myocardial infarction, heart failure, cardiac arrhythmia, and stroke (1,2). One particularly interesting study was conducted in Ontario, showing that the frequency of hospital admissions for acute myocardial infarction was much higher during the seven days after a laboratory-confirmed influenza infection than during a control period (20.0 admissions per week vs. 3.3 admissions per week; rate ratio: 6.05, 95% CI: 3.86–9.50) (3). In this study, respiratory specimens that tested for influenza infection using high-specificity methods were submitted from physician offices, emergency departments, hospitals, long-term care facilities, and public health departments as part of routine clinical care, outbreak investigations, or research, meaning a wide array of clinical presentations and infection severity. Hospitalizations for acute myocardial infarction were obtained from the Discharge Abstract Database of the Canadian Institute for Health Information. The self-controlled case-series method was applied in which only individuals who experienced an event of interest are included and are acting as their own control (risk vs. control period), meaning that time invariant confounders such as comorbidities are eliminated (4). In an ecological analysis of vital registration data in ten countries, the fraction of ischaemic heart deaths attributable to influenza was estimated at 3.9%, ranging from less than 1% to 10% according to country and year (5).

Several biological mechanisms have been proposed to explain how an infection could trigger a CVD: 1) the induction of pro-inflammatory changes in the cellular composition of atherosclerotic lesions, 2) the induction of a persistent

pro-coagulant state, including platelet activation, 3) the increased metabolic needs of peripheral tissues and organs compromising arterial perfusion, and 4) the infection and inflammation of myocardial cells disturbing the cardiac function (6,7).

Protective effect of vaccines

The protective role of influenza vaccination on CVD death was first raised by Meyers in a review of one clinical trial and three epidemiological studies published in 2003 (8). The first Cochrane review on the association between influenza vaccination and cardiovascular risk reduction was published in 2008 and updated in 2015 (9,10). We conducted a PubMed search that identified 28 systematic reviews with or without meta-analysis on the protective effect of influenza vaccination on CVD, seven of which were published in 2022–2023 (see details in the **Supplemental material**). As seen in **Table 1**, these reviews focused on different questions, and used different data sources, selection criteria, and outcomes. Most results leaned towards a protective effect as shown in the most comprehensive review covering 33 studies. Out of 52 comparisons reported in the manuscript, 40 showed a statistically significant reduction in risk, 11 showed a non-statistically significant reduction in risk, and in only one comparison, a non-statistically significant increased risk of 2% was observed for stroke (11). The evidence is particularly strong for the occurrence of cardiac events in high-risk patients, which is supported by results from four randomized clinical trials (two of high quality and two of low quality) showing a 45% decrease risk (95% CI: 25%–59%) of major adverse cardiovascular events (cardiovascular death or hospitalization for myocardial infarction, unstable angina, stroke, heart failure, or urgent coronary revascularization) among participants who had a history of coronary disease and within 12 months of follow-up (12). It should be noted that there is much overlap between risk factors for complication of influenza infection and cardiovascular disease in adults, with one exception: hypertension, a frequent condition among the adult population of Canada (24%) but not included in the Canadian Immunization Guide list of conditions for which influenza vaccination is particularly recommended (13,14).

Results of recently published studies not included in these reviews provide additional evidence. In a multicentric randomized clinical trial on the effect of inactivated influenza vaccine among patients with chronic heart failure, vaccination did not significantly reduce the first primary composite outcome (cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke) during the entire three-year trial period, whereas vaccination reduced community-acquired pneumonia by 42% (95% CI: 20%–58%). During peak influenza circulation periods, however, a statistically significant protective effect of 18% (95% CI: 1%–32%) was observed against the composite CVD outcome (23). Administrative data from the Alberta Health Care Insurance Plan were analyzed to assess the risk of stroke event comprising acute ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, and transient ischaemic attack, following influenza vaccination during the period 2009–2018. Adjusted for demographics and comorbidities, recent influenza vaccination provided a statistically significant protection of 22% (95% CI: 21%–24%) (24).

Economic analyses

Cardiovascular outcomes are rarely incorporated into economic evaluations of influenza vaccines. Hospitalizations for these outcomes have been specifically included in a few piggyback economic evaluations of high-dose inactivated influenza vaccine trials reported in a systematic review, which concluded that reduced cardiorespiratory complications were an important driver of the economic benefits of vaccination (25). Pneumonia could directly result in death or be a contributing cause of a more distant fatal outcome, but permanent sequelae are not frequent (26). The long-term consequences of adverse cardiovascular outcomes are much more severe, for stroke especially (27). In a meta-analysis of the cost effectiveness of influenza vaccination in the elderly in high-income countries, the conclusion was that incremental cost-effectiveness ratios in a societal perspective were favourable regardless of the types of vaccines (28). This is not necessarily the case when a health-system perspective is adopted. In Québec, an economic evaluation of the standard dose-inactivated influenza vaccination concluded that it was not cost-effective among the groups with chronic conditions aged 5–64 years and for healthy individuals of any age, approaching the cost-effectiveness threshold ($45,000/QALY, quality-adjusted life year, corresponding to the per capita gross domestic product in Canada in 2015) for healthy individuals aged 75 years and over (29). Accordingly, it was proposed to withdraw healthy adults aged 60–74 years from the list of groups at high-risk for influenza-associated hospitalization and death who had free access to vaccination.

The inclusion of cardiovascular outcomes in the base-case scenario (outcomes with high-level evidence) and in sensitivity analyses (outcomes with moderate-level evidence) of economic evaluation of vaccines targeting respiratory infections could change the results of economic evaluation markedly, especially for high-risk groups. This is especially important in the context of increasing availability of new-generation influenza vaccines having a higher purchase cost than older ones.

Table 1: Main characteristics of meta-analyses published in 2021–2023, and pertaining to the potential effect of influenza vaccines on cardiovascular disease in adults

Reference	Objectives	Number of studies included	Main results[a]
Diaz-Arocutipa *et al.*, 2022 (15)	To evaluate the effect of the influenza vaccine on cardiovascular outcomes in patients with coronary artery disease.	5 RCTs involving 4,211 patients	Influenza vaccine significantly reduced the risk of major adverse cardiovascular event (RR: 0.63, 95% CI: 0.51–0.77), all-cause mortality (RR: 0.58, 95% CI: 0.40–0.84) and cardiovascular mortality (RR: 0.53, 95% CI: 0.38–0.74). Reduction in the risk of myocardial infarction was not statistically significant (RR: 0.69, 95% CI: 0.47–1.02).
Maniar *et al.*, 2022 (16)	Updated meta-analysis including all RCTs that evaluated influenza vaccine and its association with cardiovascular outcomes.	8 RCTs with a total of 14,420 patients	Influenza vaccine, as compared with control/placebo, was associated with significantly lower risk of major adverse cardiovascular events at the follow-up (RR: 0.75, 95% CI: 0.57–0.97).
Gupta *et al.*, 2022 (17)	Systematic review and meta-analysis addressing whether vaccination against influenza reduces adverse vascular events and mortality in heart failure patients.	7 non-randomized studies with a total of 247,842 patients	The risk of all-cause mortality is significantly reduced within 12 months of a heart failure patient receiving the influenza vaccine (RR: 0.75, 95% CI: 0.71–0.79); very low certainty of evidence. The risk of cardiovascular-related mortality was significantly reduced (RR: 0.77, 95% CI: 0.73–0.81); low certainty of evidence. The pooled risk of all-cause hospitalization was higher among vaccinated heart failure patients (RR: 1.24, 95% CI: 1.13–1.35), based on two studies; very low certainty of evidence.
Jaiswal *et al.*, 2022 (18)	To estimate the effect of influenza vaccination on cardiovascular and cerebrovascular outcomes among patients with established CVD.	5 RCTs and 13 observational studies, with a total of 22,532,165 patients were included	At a mean follow-up of 1.5 years, the vaccinated group was associated with a lower risk of all-cause mortality (HR: 0.71, 95% CI: 0.63–0.80), major adverse cardiovascular event (HR: 0.83, 95% CI: 0.72–0.96), cardiovascular mortality (HR: 0.78, 95% CI: 0.68–0.90), and MI (HR: 0.82, 95% CI: 0.74–0.92). The incidence of stroke (HR: 1.03, 95% CI: 0.92–1.06) and heart failure (HR: 0.74, 95% CI: 0.51–1.08) did not differ between the two groups.
Behrouzi *et al.*, 2022 (12)	To evaluate if seasonal influenza vaccination is associated with a lower risk of fatal and non-fatal cardiovascular events.	6 published RCTs comprising a total of 9,001 participants	Influenza vaccination was associated with a lower risk of composite cardiovascular events (3.6% vs. 5.4%; RR: 0.66, 95% CI: 0.53–0.83). Protection was demonstrated among patients with recent acute coronary syndrome (RR: 0.55, 95% CI: 0.41–0.75) but not in those without cardiac disease history (RR: 1.00, 95% CI: 0.68–1.47).
Tavabe *et al.*, 2023 (19)	To identify studies that investigated the potential effects of the influenza vaccine on arrhythmia risk.	1 RCT with 2,532 patients and 6 observational studies with 3,167,445 patients were included	One RCT demonstrated a non-significant benefit against arrhythmia: (OR: 0.43, 95% CI: 0.11–1.64) in patients after myocardial infarction or those with high-risk stable coronary heart disease. A meta-analysis based on observational studies showed that vaccination was associated with a significantly lower risk of arrhythmia (OR: 0.82, 95% CI: 0.70–0.97).
Liu *et al.*, 2023 (20)	To investigate the relationship between receiving the flu vaccine with stroke and its hospitalization in the elderly.	14 observational studies were included for a total of 3,198,646 participants	Summary OR of occurrence and hospitalization of stroke compared to the unvaccinated group in vaccine recipients was 0.84 (95% CI: 0.78–0.90).
Addario *et al.*, 2023 (11)	To summarize the impact of vaccination against influenza, shingles, and pneumococcus on the risk of cardiovascular events in persons 65 years of age and older.	A total of 33 studies pertaining to influenza vaccination were analyzed	Out of 52 comparisons reported in the manuscript, 40 showed a statistically significant reduction in risk, 11 a non-statistically significant reduction in risk, and, in only one comparison, a non-statistically significant increased risk of 2% was observed. Also, repeated influenza vaccination showed a consistent and dose-dependent protective effect against acute coronary syndromes and stroke.
Gupta *et al.*, 2023 (21)	To provide evidence regarding the protective effects of influenza vaccination in patients with cardiovascular disease.	15 studies with a total of 745,001 patients were included in the analysis, including 6 RCTs, 7 retrospective cohort studies, and 2 case-control studies	Lower rates of all-cause mortality (OR: 0.74, 95% CI: 0.64–0.86), cardiovascular death (OR: 0.73, 95% CI: 0.59–0.92), and stroke (OR: 0.71, 95% CI: 0.57–0.89) were observed. There was no significant statistical difference in rates of myocardial infarction (OR: 0.91, 95% CI: 0.69–1.21) or heart failure hospitalizations (OR: 1.06, 95% CI: 0.85–1.31).
Modin *et al.*, 2023 (22)	Meta-analysis of RCTs to assess the effect of influenza vaccination on the incidence of cardiovascular events in patients with ischaemic heart disease or heart failure.	5 peer-reviewed RCTs and 1 non-peer-reviewed RCT, for a total of 9,340 patients, were included. The primary endpoint was a composite of cardiovascular death, acute coronary syndrome, stent thrombosis or coronary revascularization, stroke or heart failure hospitalization	Influenza vaccination was associated with a reduced incidence of the primary composite endpoint (random effects HR: 0.74, 95% CI: 0.63–0.88, $p<0.001$, I2=52%), cardiovascular death (rHR: 0.63, 95% CI: 0.42–0.95, $p=0.028$, I2=58%) and all-cause death (rHR: 0.72, 95% CI: 0.54–0.95, $p=0.0227$, I2=52%).

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; rHR, randomized hazard ratio; RR, risk ratio
[a] Vaccine efficacy/protection=(1 RR/HR/OR) expressed as a percentage

Promotion of vaccination

Results from the 2021–2022 Seasonal Influenza Vaccination Coverage Survey showed that overall uptake in the adult population was 39%, reaching 71% among seniors 65 years of age and older but only 38% among adults aged 18–64 years with a chronic medical condition, well below the national coverage goals of 80% (30). In 2021, the American College of Cardiology and the World Heart Federation published a statement focusing on the effect of influenza vaccines on CVD (4). Although the importance of the CVD protection may be well known by cardiologists, it is certainly not the case in the Canadian public health network, as it is not mentioned in the most recent statement on seasonal influenza vaccination (2022–2023) of the National Advisory Committee on Immunization nor in the Canadian Immunization Guide (14).

In Denmark, a cluster-randomized trial was conducted during the 2022–2023 influenza season among about one million citizens aged 65 years and older (31). Households were randomly assigned to usual care, or were sent nine different short electronic letters, designed on the basis of different behavioural concepts. Compared with usual care, influenza vaccination rates were higher in the group that received an electronic letter that highlighted the potential cardiovascular benefits of vaccination (81.00% vs. 80.12%; difference 0.89% points [95% CI: 0.29–1.48]). Other letters that did not highlight the potential cardiovascular benefits of vaccination (7 out of 9) were ineffective, except for the one that provided a reminder. Although the magnitude of the effect of this ultra-light intervention was modest, this is a "proof-of-concept" that elderly individuals are receptive to information about their risk of cardiovascular disease. More research is needed to assess the field impact of CVD messaging provided by healthcare providers including family physicians and pharmacists.

Conclusion

The available evidence of a protective effect of influenza vaccines on CVD outcomes is sufficiently robust to include this effect in future economic evaluations. To mention this potential effect may change the perception of the population on the usefulness of influenza vaccines and increase vaccine uptake. Messages prepared by public health authorities and information provided to patients by vaccinators, including family physicians, nurses and pharmacists, should contain updated information on this issue. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus, and *Streptococcus pneumoniae* infections can also trigger adverse cardiovascular outcomes that may be prevented by vaccination (3,32,33). The evidence is robust for COVID vaccines but not for pneumococcal vaccines, due to the absence of high-quality studies. The evidence is still to be collected for the new respiratory syncytial virus vaccines for adults that will be marketed in the near future.

Authors' statement

The authors contributed equally to the conceptualization of the manuscript, data collection and analysis, interpretation of data, and writing of the manuscript.

Competing interests

None to report.

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Supplemental material

These documents can be accessed on the Supplemental material file.

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Infectious syphilis and congenital syphilis in Canada, 2022*

INFECTIOUS SYPHILIS

There were **13,953 cases** of infectious syphilis** reported in 2022, corresponding to a **rate of 36.1 cases per 100,000 population**

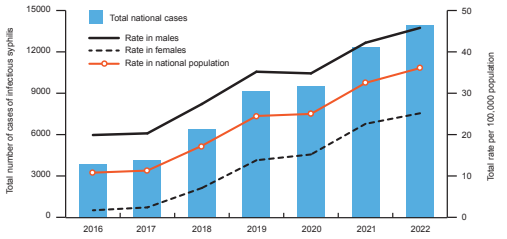
- **11% rate increase since 2021**
- **109% rate increase since 2018**‡

CONGENITAL SYPHILIS

There were **117 cases** of confirmed early congenital syphilis** reported in 2022, corresponding to a **rate of 31.7 cases per 100,000 live births**

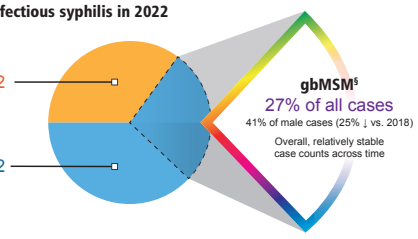
- **7% rate increase since 2021**
- **599% rate increase since 2018**‡

Number of reported cases and rates of infectious syphilis by sex in Canada, from 2016 to 2022

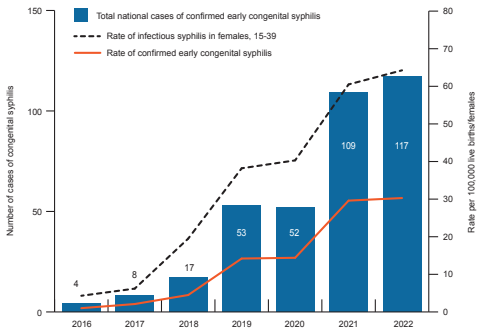


Total national cases and rates include reported cases among males, females, transgender individuals and those of other or unknown sex.

Cases of infectious syphilis in 2022

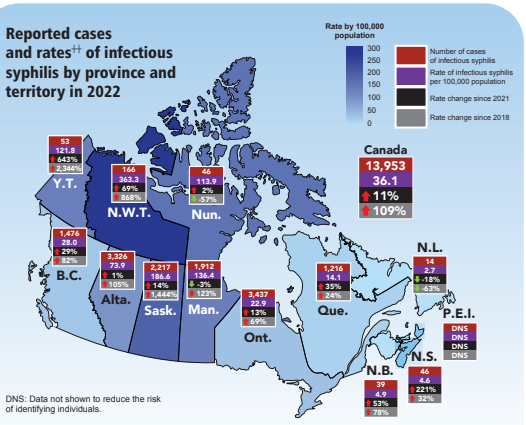


Number of reported cases and rates of confirmed early congenital syphilis and rates among females aged 15-39 years in Canada, from 2016 to 2022



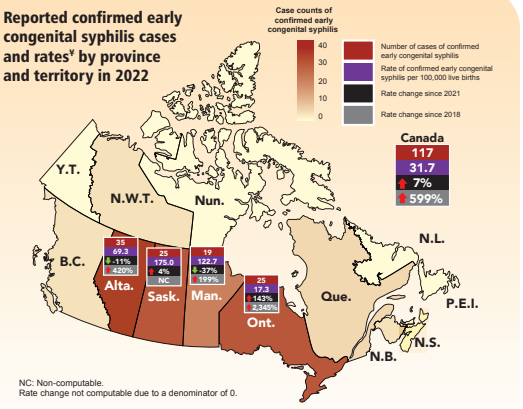
In 2022, there were at least 246 reported cases of congenital syphilis,‡ which includes confirmed early congenital syphilis, probable early congenital syphilis, syphilitic stillbirth, and unknown-stage congenital syphilis.

Reported cases and rates‡‡ of infectious syphilis by province and territory in 2022



DNS: Data not shown to reduce the risk of identifying individuals.

Reported confirmed early congenital syphilis cases and rates¥ by province and territory in 2022



NC: Non-computable.
Rate change not computable due to a denominator of 0.

Rates between 2020 and 2022 occurred in the context of the COVID-19 pandemic, which included a period of decreased demand for and access to sexually transmitted and blood-borne infection (STBBI) services.¥

Social and structural determinants of health and health inequities play a role in the inequitable occurrence of syphilis across different populations.‡‡

Syphilis screening and timely treatment are essential to prevent transmission and complications. Find PHAC's recently updated syphilis screening recommendations in the STBBI Guides for Health Professionals.

* Data were directly obtained from provinces and territories (PTs) through both routine and enhanced surveillance systems for syphilis. Due to periodic updates of surveillance data, counts and rates may change over time. In cases of discrepancy between data reported by PHAC and those reported by individual PTs, PT data should be considered more accurate as they are the most current.

** Infectious syphilis includes the primary, secondary, early latent and infectious neurosyphilis (less than one year after infection) stages of infection, during which syphilis is transmissible. Confirmed early congenital syphilis is defined as a laboratory confirmation of infection by *Treponema pallidum* occurring within the first 2 years of birth. Reference: Case definitions for diseases under national surveillance. *Can Comm Dis Rep* 2000;26(S3). Retrieved August 2023, from https://www.canada.ca/en/public-health/services/diseases/syphilis/health-professionals/national-case-definition.html

† Rates are calculated against a 2018 benchmark to align, for comparability purposes, with Government of Canada commitments in 2018† to World Health Organization (WHO) 2030 global STBBI targets.† The targets include a 90% reduction of syphilis incidence and 50 or fewer cases of congenital syphilis per 100,000 live births. (1) Public Health Agency of Canada. (2018) Reducing the health impact of sexually-transmitted and blood-borne infections in Canada by 2030: A pan-Canadian STBBI framework for action. https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/reports-publications/sexually-transmitted-blood-borne-infections-action-framework.html (2) World Health Organization. (2016). Global health sector strategy on sexually transmitted infections 2016-2021: toward ending STIs. World Health Organization. https://apps.who.int/iris/handle/10665/246296

¥ Survey of the impact of COVID-19 on the ability to provide STBBI prevention, testing and treatment including harm reduction services in Canada. Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control. 2022. https://www.canada.ca/en/public-health/services/publications/diseases-conditions/survey-impact-covid-19-delivery-stibbi-prevention-testing-treatment.html

§ gbMSM: Gay, bisexual, and other men who have sex with men. Note that only 8 PTs (B.C., Alta., Sask., Ont., N.B., N.S., Y.T., N.W.T.) have consistently submitted data on cases among gbMSM since 2018, therefore only these PTs are included in calculations of gbMSM proportions. Data on other priority populations are not currently available for analysis.

‡‡ Aho J, Lybeck C, Tetteh A, Issa C, Kouyoumdjian F, Wong J, Anderson A, Popovic N. Rising syphilis rates in Canada, 2011–2020. *Can Comm Dis Rep* 2022;48(2/3):52–60. https://doi.org/10.14745/ccdr.v48i23a01

‡‡ Caution should be used when comparing rates across PTs. Reported rates in PTs with a relatively small population size are prone to fluctuation and instability due to small changes in case count for small population denominators resulting in large rate changes. To contextualize rates, it is also important to look at the case counts per province and territory.

¥ Rate changes for congenital syphilis should be interpreted with caution as changes in case counts based on small denominators are subject to fluctuation and instability, resulting in large rate changes. Congenital syphilis case counts should therefore always be taken into context when interpreting rate changes.

‡ Canada does not currently have a national case definition for probable early congenital syphilis, syphilitic stillbirth, or unknown/unspecified-stage congenital syphilis. Data for these cases are submitted according to each PT's own case definitions. Currently, only Alta., Sask. and Man. have case definitions for probable early congenital syphilis and syphilitic stillbirth. B.C. and Que. have case definitions for both confirmed and probable early congenital syphilis that include stillbirths, while Y.T. has a case definition for confirmed cases only of early congenital syphilis that includes stillbirths. In addition, the N.W.T. have a case definition for syphilitic stillbirth, but not for probable early congenital syphilis.

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Characteristics and clinical outcomes of nirmatrelvir/ritonavir (Paxlovid™) recipients in Canada, 2022: a descriptive cohort study

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Abstract

Background: Nirmatrelvir/ritonavir (N/R) (Paxlovid™) was introduced in Canada in January 2022. This was the first oral coronavirus disease 2019 (COVID-19) antiviral therapy that was deployed on a large scale in Canada. Since N/R was a new therapeutic option to reduce severe outcomes in high-risk populations, clinical and implementation questions were raised about its real-world utilization and impact. The objective of this retrospective observational study was to describe the characteristics and clinical outcomes of recipients of N/R in the first several months of its availability in Canada, during the Omicron wave.

Methods: Provincial summary data were pooled together for the analysis. Descriptive statistics were used to explore the characteristics and clinical outcomes of the recipients. Pearson's Chi-square test and unadjusted odds ratio along with 95% confidence intervals were used to identify the potential risk factors for severe outcomes. Data were generally collected between January and September 2022.

Results: Seventy-six percent of N/R recipients were 60 years of age and older and 56% were female. Eighty-four percent of recipients had received three or more COVID-19 vaccinations and 67% had comorbidities. All-cause severe 30-day outcomes were uncommon, with 0.4% reported as deceased, 0.1% admitted to the intensive care unit and 2.0% hospitalized after N/R administration. Risk factors statistically associated with severe outcomes were immunosuppression, comorbidities, age of 60 years and older, and being unvaccinated.

Conclusion: In the first months of its availability in Canada, N/R was mostly used in vaccinated patients 60 years and older with one or more comorbidities. Severe outcomes in N/R recipients were uncommon and mostly reported in patients with risk factors.

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Introduction

On January 17, 2022, nirmatrelvir/ritonavir (N/R or Paxlovid™) was authorized by Health Canada (1) as the first oral antiviral coronavirus disease 2019 (COVID-19) treatment for adults who had mild to moderate symptoms, had positive severe acute respiratory syndrome coronavirus 2 viral test results, and were at high risk for progression to severe COVID-19, namely hospitalization or death. The regulatory approval was supported by the interim results of the manufacturer's phase 2/3 randomized controlled trial, which assessed efficacy and safety in high-risk unvaccinated adults prior to the emergence of Omicron variants of concern. Participants in this study were eligible if they had at least one characteristic or coexisting condition associated with high risk of progression to severe COVID-19 (such as age of 65 years and older, smoking, diabetes, hypertension, immunosuppression, cardiovascular, pulmonary or kidney diseases, etc.) The results of this study demonstrated an 89% reduction in the composite outcome of COVID-19-related hospitalization or all-cause death from 6.4% to 0.78%

(95% confidence interval [CI]: −7.21%–−4.03%) through a 28-day follow-up when treated within five days of symptom onset, compared to placebo. In subgroup analyses, the reduction of COVID-19-related hospitalizations or all-cause death was shown to be of lower magnitude in patients younger than 65 years old (−4.35, 95% CI: −5.91–−2.79) compared to those 65 years and older (−13.93, 95% CI: −20.07–−7.80) or in those with 0–1 comorbidities (−4.76, 95% CI: −6.36–−3.16) compared to those with 2–3 comorbidities (−8.96, 95% CI: −13.59–−4.32) (2).

Given the fast-changing nature of the COVID-19 pandemic, questions were raised about the applicability of these study results in vaccinated patients and with new variants (e.g. Omicron). In addition, safety considerations of N/R included drug-drug interactions with several medications commonly used to manage comorbidities that can be associated with increased risk of COVID-19 severity, thus potentially constraining the use of N/R in some patient groups.

With limited "real world" experience with N/R in the Canadian context of highly vaccinated populations and new variants, evaluation of N/R usage was considered a priority by several stakeholders. As such, in collaboration with representatives from provinces, territories, some federal departments and clinical experts, the Public Health Agency of Canada (PHAC) developed an evaluation framework, where one of the components of the evaluation aimed to document the characteristics of the recipients of N/R in Canada and their outcomes, which are reported here. At the time when this study was initiated, the effectiveness of N/R in vaccinated patients was unknown.

The Public Health Agency of Canada assumed a leadership role in this evaluation, which is consistent with two of its mandates: to respond to public health emergencies and to strengthen intergovernmental collaboration on public health and facilitate national approaches to public health policy and planning.

The objectives of this evaluation were to describe the characteristics and clinical outcomes at 30 days for recipients of N/R in the first several months of its availability in Canada.

Methods

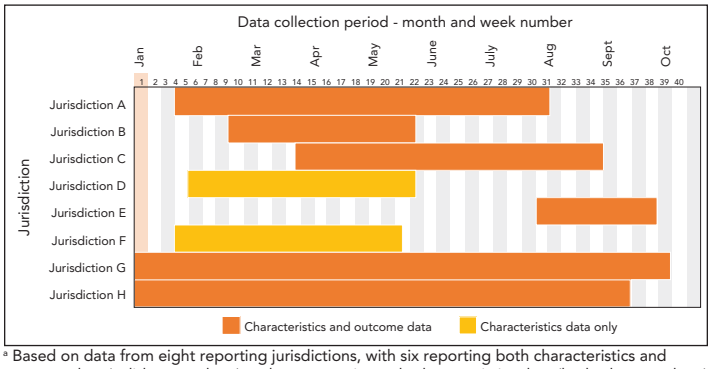
An evaluation framework was developed in collaboration with clinical experts and federal and provincial representatives at the onset of the N/R rollout to answer questions regarding the characteristics (demographics and risk factors) and 30-day outcomes of N/R recipients using a descriptive cohort design. A descriptive study design was selected given the variability of available information across jurisdictions and complexity of establishing a standardized denominator that would have been needed for a cohort study. Seven provinces and one federal department contributed aggregated data for this evaluation, representing 74% of the Canadian population.

Sources of data and variables

A data dictionary defining variables was prepared and used by participating jurisdictions following consultations. Jurisdictions may have interpreted the definition of the variables according to the criteria generally used in their administrative healthcare data systems. Data collection methodologies varied by jurisdiction and, in several jurisdictions, over time. Jurisdictions used one of three methodologies to collect characteristic and outcome data for N/R recipients within their jurisdictions: primary data collection typically conducted by telephone or online questionnaires; secondary data collection from pre-existing health databases or chart reviews; or a combination of both methods. Most jurisdictions used health databases, such as drug benefit, immunization registry and hospital discharge information systems, to obtain the data. Questionnaires and chart reviews were sometimes used to obtain information about the clinical outcomes when not available in the information systems.

Dates for data collection varied by jurisdiction depending on availability of information, but generally data were collected between January and September 2022. The availability and timeliness of information related to N/R recipient characteristics and clinical outcomes also varied by jurisdiction and within jurisdictions due to changes in the N/R programming over time, including eligibility criteria and accessibility. Six jurisdictions reported characteristics and outcome information, while two reported only characteristics information. The length of the data collection period ranged from nine to 39 weeks, with a median data collection period of 19 weeks. Not all jurisdictions were able to contribute data for all variables (**Figure 1**).

Figure 1: Data collection period by jurisdiction, evaluation of nirmatrelvir/ritonavir (Paxlovid™) recipient characteristics and clinical outcomes, Canada[a], 2022



[a] Based on data from eight reporting jurisdictions, with six reporting both characteristics and outcome data (solid orange bars) and two reporting only characteristics data (hashed orange bars)

Outcomes were assessed at 30 days following the first day of N/R treatment. Severe outcomes, notably hospitalization, intensive care unit (ICU) admission and death, were measured as all-cause. Hospitalizations and death were chosen because one of the goals of the COVID-19 therapeutics response is to protect the population and the healthcare system by preventing hospitalizations and deaths. All-cause outcomes were used

due to the feasibility of attributing COVID-19 cause in most participating jurisdictions' data systems.

Participating jurisdictions used an aggregate summary table to report results and dates of collection. Summary tables from jurisdictions were submitted to PHAC between August 15, 2022, and November 8, 2022.

Analyses

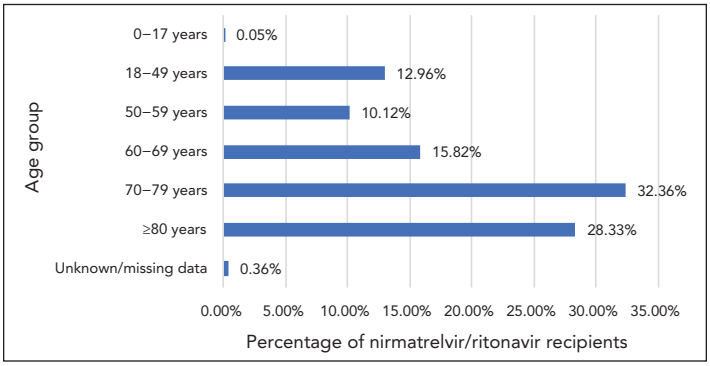
Summary table results from different jurisdictions were collated and analyzed by staff at the PHAC. Descriptive statistics were used to explore the characteristics and clinical outcomes of N/R recipients. To identify the potential risk factors for severe outcomes (hospitalized, admitted to ICU or death), Pearson's Chi-square test was used to assess the association between each of the categorical variables and severe outcomes. Again, the unadjusted odds ratio (OR) along with the 95% CI were used to describe the direction and strength of the association between risk factors and severe outcomes. The OR represents the odds that an outcome will occur in one group compared to the odds of the outcome occurring in another group. Note that due to the lack of line list data, we could not calculate the adjusted ORs. Comparisons of jurisdictions were not conducted due to the variability in eligibility criteria to N/R and possible variations in data sources or definition. All statistical analyses were performed using R software (version 4.1.3).

Results

Characteristics of nirmatrelvir/ritonavir recipients in Canada

Age group and sex information were available for 61,413 patients: 77% of N/R recipients were 60 years of age and older, while 61% were 70 years of age and older (**Figure 2**). Fifty-six percent of N/R recipients were female.

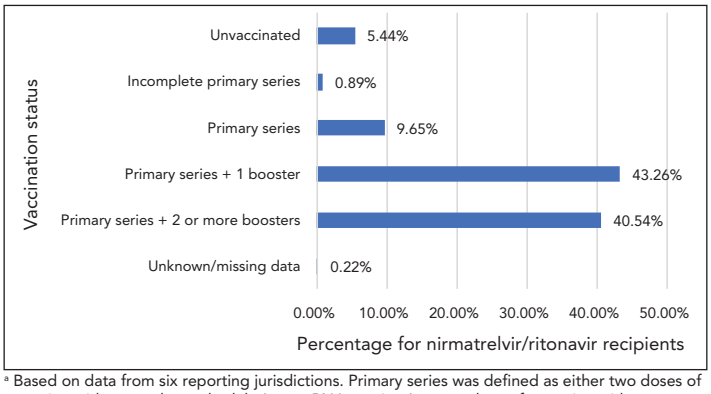
Figure 2: Age distribution of nirmatrelvir/ritonavir (Paxlovid™) recipients, Canada[a], 2022 (n=61,413)



[a] Based on data from eight reporting jurisdictions

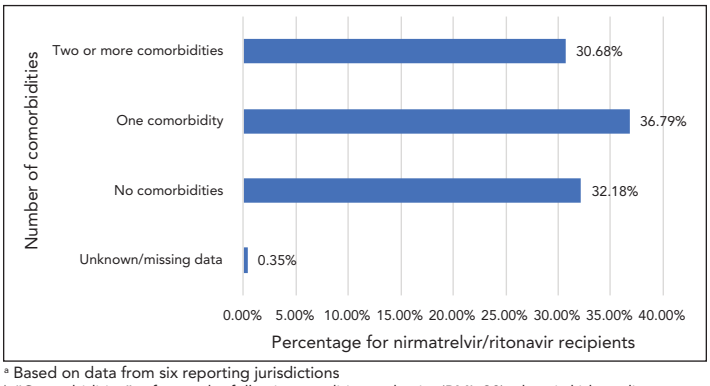
Data on vaccination status (**Figure 3**) and number of comorbidities (**Figure 4**) were available for 59,452 N/R recipients across seven jurisdictions: 84% of recipients had received three or more COVID-19 vaccinations, while only 5% were unvaccinated.

Figure 3: Distribution of vaccination status for nirmatrelvir/ritonavir (Paxlovid™) recipients, Canada[a], 2022 (n=59,452)



[a] Based on data from six reporting jurisdictions. Primary series was defined as either two doses of a vaccine with a two-dose schedule (e.g. mRNA vaccines) or one dose of a vaccine with a one-dose primary series (e.g. Janssen Jcovden® COVID-19 Vaccine). Incomplete primary series was defined as having received at least one COVID-19 vaccine but not meeting the requirements to have been considered as having completed the primary series, as per information in immunization records

Figure 4: Distribution of the number of comorbidities in nirmatrelvir/ritonavir (Paxlovid™) recipients, Canada[a,b], 2022 (n=59,452)



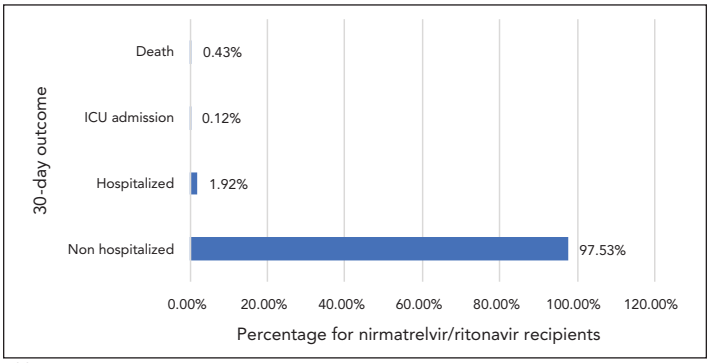
[a] Based on data from six reporting jurisdictions
[b] "Comorbidities" refers to the following conditions: obesity (BMI≥30), chronic kidney disease, diabetes, heart disease, hypertension, congestive heart failure, chronic respiratory disease including cystic fibrosis, cerebral palsy, intellectual disability, sickle cell disease, moderate or severe kidney disease (eGFR<60 mL/min), and moderate or severe liver disease (e.g. Child Pugh, Class B or C cirrhosis)

Sixty-seven percent of recipients were identified as having one or more co-morbidities, while 5.8% were assessed as being immunocompromised. Data on additional factors associated with N/R administration were available for a subset of patients. Ninety-four percent (n=13,752/14,638) of recipients were symptomatic prior to COVID testing, and 95.5% (n=11,582/12,129) received N/R within five days of testing positive. Nine percent (n=1,689/19,196) of recipients received other COVID-19 therapeutics in addition to N/R.

Clinical outcomes at 30 days following first day of treatment with nirmatrelvir/ritonavir

Of the 58,881 recipients for whom outcome data were available, 97.5% were not hospitalized for any reason in the 30-day period post-N/R administration. All-cause severe outcomes were uncommon, with 0.4% (n=243) reported as deceased, 0.1% (n=67) admitted to the ICU and 2.0% hospitalized in the first 30 days after N/R administration (**Figure 5**).

Figure 5: Distribution of 30-day outcomes for patients receiving nirmatrelvir/ritonavir (Paxlovid™), Canada[a], 2022 (n=58,881)



Abbreviation: ICU, intensive care unit
[a] Based on data from six reporting jurisdictions

Table 1 presents a comparison of risk factors between subjects who experienced severe outcomes (hospitalized, admitted to ICU or death) and those who did not. The risk factors that showed a statistically significant association with severe outcomes (p<0.0001) include immunosuppressed status, vaccination status, age, sex and number of comorbidities. The odds/risk of having a severe outcome was significantly higher for patients who were immunocompromised (OR=3.79, 95% CI: 3.28–4.37, against non-immunocompromised), unvaccinated or partially vaccinated (OR=1.91, 95% CI: 1.62–2.26, against completed primary series or completed primary series with one or more booster dose), older age (60 years and older) (OR=1.64, 95% CI: 1.42–1.89, against age younger than 60 years), males (OR=1.25, 95% CI: 1.12–1.39, against females), and with one or more comorbidities (OR=1.97, 95% CI: 1.73–2.24, against no comorbidity).

Table 1: Risk factors associated with severe outcomes for patients dispensed nirmatrelvir/ritonavir (Paxlovid™), Canada[a], 2022

Risk factor	Percentage with severe outcomes	Odds ratio (95% CI)	*p*-value[b]
Immunosuppressed status			
Immunosuppressed	7.78	3.79 (3.28–4.37)	<0.0001
Not immunosuppressed	2.18	Reference	
Vaccination status			
Unvaccinated/ incomplete primary series	4.37	1.91 (1.62–2.26)	<0.000
Primary series/ primary series with one or more booster	2.33	Reference	
Age			
60 years and older	2.69	1.64 (1.42–1.89)	<0.0001
0–59 years	1.64	Reference	
Sex			
Male	2.73	1.25 (1.12–1.39)	<0.0001
Female	2.20	Reference	
Number of comorbidities			
One or more	2.92	1.97 (1.73–2.24)	<0.0001
None	1.50	Reference	

[a] Based on data from six reporting jurisdictions
[b] The *p*-values were obtained from Pearson's Chi-squared test. Primary series was defined as either two doses of a vaccine with a two-dose schedule (e.g. mRNA vaccines) or one dose of a vaccine with a one-dose primary series (e.g. Janssen Jcovden® COVID-19 Vaccine). Incomplete primary series was defined as having received at least one COVID-19 vaccine but not meeting the requirements for being considered having completed the primary series as per information in immunization records. The term "immunosuppressed" was defined as individuals meeting the following criteria: receipt of treatment for solid tumours and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment); receipt of solid-organ transplant and taking immunosuppressive therapy; receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within two years of transplantation or taking immunosuppressive therapy); moderate or severe primary immunodeficiency (e.g. DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome); advanced or untreated HIV infection; and/or active treatment with high-dose corticosteroids (i.e. 20 mg or more prednisone or equivalent per day when administered for two or more weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumour-necrosis factor (TFN) blockers, and other biological agents that are immunosuppressive or immunomodulatory

Discussion

In the first months of its availability in Canada, the results of this descriptive cohort showed that N/R was mostly used in vaccinated patients (83.80% had received three or more doses) and patients over 60 years of age (76.51%); 30.68% were reported as having two or more comorbidities. In contrast, the study participants included in the phase 2/3 randomized controlled trial that supported the regulatory approval were unvaccinated, had a median age of 46 years and 61% had two or more characteristics or coexisting conditions placing them at high risk of progression to severe disease (2). The definitions of coexisting conditions and the methodology used for data collection differed in both studies making direct comparisons of the characteristics of the study populations difficult.

This study estimated that 2.5% of N/R recipients progressed to develop all-cause severe outcomes (hospitalization, ICU admission or death). A 0.4% all-cause mortality was also seen in N/R recipients. These rates of severe outcomes are slightly higher than in other published studies that reported severe outcome rates of less than 1% (1,3,4) or death rates of less than 0.4% (4–6). As well, a recent retrospective cohort study in the United States observed a 0.47% COVID-19-related hospitalization rate and a 0.01% mortality rate among recipients

of N/R (7)—results that were also lower than those observed in this study. A recent study from Ontario observed a 2.1% risk of hospitalization for COVID-19 or death at 30 days for patients treated with N/R (8).

These differences may be explained by the methodology used in our evaluation: we measured all-cause outcomes, while other studies measured COVID-19-specific outcomes. Additionally, recipients of N/R in Canada tended to be older (1,5,6) than other study populations, which may account for those studies' lower severity rates. Many studies also followed patients for longer periods of time than the 30-day period in this evaluation or assessed COVID-19-specific severe outcomes, which made comparisons to this evaluation difficult. Furthermore, other studies used case-control study designs with various methods to control bias whereas this study was a descriptive cohort.

In this evaluation, severe outcomes were relatively rare and were highest in the following groups: the immunocompromised; the unvaccinated/partially vaccinated; those having one or more comorbidities; those aged 60 years or older; and males. These results are consistent with those who have been identified as being most at risk for severe outcomes (9) and thus would benefit the most from N/R. Since this evaluation did not include a comparison group, the evaluation was unable to determine benefit of N/R in preventing higher rates of severe outcomes.

Limitations

This evaluation has several limitations. Characteristics and clinical outcomes of N/R recipients were assessed in jurisdictions that self-selected to participate in this evaluation. As only aggregate level data were collected, it was not possible to conduct sub-analyses nor assess for any confounding or interaction effects among the characteristics with respect to the outcomes. Data from multiple jurisdictions were aggregated to form a national dataset although there were variations in the distribution of clinical outcomes by patients' characteristics across the different jurisdictions. We could not account for the dissimilarities in the data from each jurisdiction. Data collection periods and eligibility criteria varied by jurisdiction and by time, which may have impacted the description of the characteristics. For example, early on when N/R supply was limited and criteria were stricter, patients may have been older and at higher risk for severe outcomes. Participation by jurisdictions was voluntary. Although the jurisdictions that did participate represented a significant percentage of the Canadian population (74%), this evaluation may not be fully representative of all N/R recipients in Canada. It is well established that COVID-19 disproportionately affects racialized and marginalized populations (10); however, as ethnicity data were not available for this evaluation, the impact of ethnicity on outcomes among N/R recipients was not assessed. Finally, the results of this evaluation may have underestimated the proportion of patients who did not experience a severe outcome as it is possible that some patients were included who may never have started or may not have completed treatment but were deemed "N/R recipients."

Conclusion

Despite its limitations, these findings were useful in providing an assessment of who has received N/R in the first months of its availability in Canada and provided information about the low rate of severe outcomes in mostly vaccinated N/R recipients at the national level. While awaiting results from adaptive platform trials or other randomized controlled studies on the real-world effectiveness of N/R, which will require more time to perform, this evaluation provided participating jurisdictions with useful information to inform decision-making with respect to N/R programming and policies in the interim. As more COVID-19 therapeutics are developed and become available, similar questions may arise. The collaborative model used for this evaluation project could be employed in the future to answer similar questions with other therapies; however, it should preferably strive to include a comparison group in the methodology, which would enable adjusting for confounders and assessing effectiveness.

Authors' statements

NS — Supervision, conceptualization, methodology, data interpretation, writing–original draft, writing–review & editing
SS — Project management, conceptualization, methodology, interpretation, data curation, writing–original draft, writing–review & editing
MM — Data analysis, methodology, data organization, statistical analysis, interpretation, writing–original draft, writing–review & editing
PD — Conceptualization, methodology, writing–original draft, writing–review & editing

Competing interests

None.

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Current and future burden from Lyme disease in Québec as a result of climate change

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Abstract

Context: Environmental changes will foster the spread of *Ixodes scapularis* ticks and increase the incidence of Lyme disease in Québec in the coming years. The objective of this study is to estimate the epidemiological and clinical burden and part of the current economic burden of Lyme disease in Québec and to estimate the number of cases expected by 2050.

Methods: Cases of Lyme disease reported in Québec from 2015 to 2019 were used to describe their demographic, geographical and clinical characteristics and the cost of their initial care. Three incidence rate scenarios were then developed to estimate the number of cases expected by 2050, based on demographic and climate projections.

Results: From 2016 to 2019, 1,473 cases of Lyme disease were reported in Québec. Over 90% of those cases were acquired in two regions of southern Québec (Estrie and Montérégie), while the individuals infected were residents from all over Québec. The average age of cases is 44 years and 66% of infections were at the localized stage, the first stage of Lyme disease. The cost of initial care is estimated at an average of $182 CAN per patient ($47 CAN at the localized stage and $443 CAN at the disseminated stage). According to projections, over 95% of the Québec population will live in a climate zone conducive to the establishment of ticks by 2050, with a number of cases acquired in Québec being 1.3 to 14.5 times higher than in 2019, depending on the incidence rate scenario used.

Conclusion: The epidemiological burden is concentrated primarily in southern Québec, but the clinical and economic burden is already distributed throughout the province. The projections for 2050 should help the regions of Québec adapt and optimize public health protection measures.

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Introduction

Cases of Lyme disease have been on the rise for several years in Québec, as in the rest of Canada (1). This trend is expected to continue with expected climate and environmental changes (2). However, the burden of Lyme disease, namely its epidemiological, clinical and economic characteristics (3), is still poorly documented in Québec.

Lyme disease, caused by the bacterium *Borrelia burgdorferi*, is transmitted by the *Ixodes scapularis* tick in eastern North America. The infection evolves in three clinical stages: the localized stage, characterized by erythema migrans; the early disseminated stage, with systemic, neurological or cardiac symptoms; and the late disseminated stage, characterized primarily by Lyme arthritis (4). Rising temperatures linked to climate and environmental change are expected to favour the survival of tick populations, extend tick activity over the year and foster the establishment of tick populations in new geographic areas, at the same time as there is an increase in the distribution area of hosts such as the white-tailed deer or white footed mice (2). As a result, the season and zone for human exposure to ticks, and thus the incidence of Lyme disease in Québec, is expected to increase over time.

Lyme disease has been a notifiable disease (ND) in Québec since 2003 (1). The demographic and geographic characteristics of cases are published annually by the *Institut national de santé publique du Québec and the Ministère de la Santé et des Services sociaux* (1,5). Several studies have described the clinical picture of Lyme disease, but only for some regions of Québec (6–14). Some costs associated with Lyme disease have been assessed in Ontario (15) and the United States (16–20), but their results cannot be transposed directly to Québec due to differences in healthcare systems. To our knowledge, only two studies have estimated the number of cases and the anticipated costs based on climate change (21,22). The most recent study, conducted by the Canadian Institute for Climate Choices (CICC), estimates that there will be 8,500 new cases of Lyme disease each year in Canada by the middle of the century (3,000 in Québec), for an annual cost of $3M in health expenditures (22). However, those studies are not based on surveillance data from Québec, which limits their interpretation.

Our study describes the current burden of Lyme disease in Québec, from an epidemiological and clinical perspective, based on human surveillance data. Exposure to ticks was also considered to have a broader view of the burden for the province, based on acarological surveillance data. Moreover, to add an economic dimension to the burden, the direct cost to the healthcare system for initial care and hospitalization of cases was calculated. Finally, the number of expected cases by 2050 was also estimated, taking into account various demographic, climate and incidence rate scenarios.

Methods

Data source

Human cases of Lyme disease

Human cases of Lyme disease reported in Québec by physicians or laboratories between January 1, 2015, and December 31, 2019, were extracted from the registry of NDs (1). As the ND does not include clinical data for our study period, that data was found in the reports available from the public health departments (Direction de santé publique [DSPu]) in Estrie (n=105 cases in 2017), Montérégie (n=231 cases in 2016–2018) and Montréal (n=69 cases in 2016–2017). These reports present some results from epidemiological investigations of cases reported between 2016 and 2018 (8–11,23,24), such as stage and clinical signs, proportion of cases hospitalized and length of hospitalization. Data published by Musonera *et al.*, (14), analyzing the medical records of cases reported and treated at a hospital in Estrie and Montérégie between 2004 and 2017 (n=272), were also considered in estimating some clinical criteria not available in the ND (proportion of cases by clinical stage, proportion of cases hospitalized and length of hospitalization).

Exposure to *Ixodes scapularis* ticks

Data on the people who reported an *I. scapularis* tick in Québec between January 1, 2015, and December 31, 2019, is from the passive acarological surveillance program managed by the *Laboratoire de santé publique du Québec* (1). That laboratory receives and identifies ticks collected from humans that are voluntarily submitted by physicians. The *I. scapularis* ticks are then sent to the National Microbiology Laboratory to check for the presence of *B. burgdorferi* and other pathogens (1). To be sure of the tick exposure location, people who have travelled outside their home municipality in the 14 days prior to the bite and those whose travel history was unknown were excluded from the geographic analyses.

Cost of initial care and hospitalization

Only the direct costs to the healthcare system, i.e. the cost of initial care for the case (consultation and treatment) and hospitalizations, were considered in this study. The cost of initial care of a case is based on the cost of medical consultations in Québec published by the *Régie de l'assurance maladie du Québec* (RAMQ) (25,26) and the cost of initial treatment published by the *Institut national d'excellence en santé et en services sociaux* (INESSS) (27). The cost of hospitalizations is based on data for Québec from the Canadian Institute for Health Information (28).

Demographic projections

The current population of Québec was estimated based on the 2016 census (29). The projections are from the demographic trends published by the *Institut de la statistique du Québec*, with a moderate scenario, a low scenario and a high scenario, to estimate the possible evolution of Québec's population by 2050 (30).

Climate projections

Temperature is a significant factor in the establishment of tick populations (31–39). The threshold of 2,800 degree-days (dd) >0°C over a year was validated in several studies as an indicator of areas where *I. scapularis* ticks can survive in Québec (32,40) and was used as an indicator in our study. The annual accumulation of >0°C dd between 2009 and 2100 (average: over 30 years) for all of Québec (10 km x 10 km grid) is from the Climate Data portal (41), for greenhouse gas emission scenarios RCP 4.5 (moderate emissions scenario) and RCP 8.5 (high emissions scenario).

Analyses

Epidemiological and clinical portrait

The epidemiological portrait looked at all cases of Lyme disease reported in Québec in the ND and all persons who reported a tick to the surveillance program between 2015 and 2019, that is, the number of cases by age, sex, likely region of acquisition or

exposure to ticks, region of residence and month in which the first symptoms appeared or of exposure to ticks.

To prepare a clinical portrait of cases reported during our study period, the data published by the DSPu (8–11,13,23,24) and by Musonera *et al.* (14,42) for the Estrie, Montérégie and Montréal regions were used. The average percentages of cases by stage and clinical signs was estimated based on these data, and the percentages were related to all cases reported in Québec between 2015 and 2019 to estimate the number of cases by stage and clinical signs during our study period. Chi-squared tests (p-value=0.05) were conducted in R software (R version 4.0.2) to compare categorical variables. The cases reported and the persons who reported a tick to passive surveillance were mapped by likely region of acquisition or exposure using QGIS (version 3.14.1).

Cost of initial care and hospitalization

The cost of care was calculated by reported case and by clinical stage. Initial care includes the first medical consultation with a physician and the initial treatment prescribed based on the clinical signs. At the localized stage, a consultation with a general practitioner is recorded, while consultations are recorded at the disseminated stage with a general practitioner and for a visit and follow-up with a specialist. The initial treatment considered is the treatment recommended by INESSS (27). Two studies indicate that the prescribed treatment in Québec is appropriate in over 85% of cases (14,24). The cost of hospitalizations was estimated separately taking into account the average length and the cost of a stay.

Projected number of cases expected by 2050

All municipalities in Québec were ranked as favourable or unfavourable to the establishment of ticks based on the threshold of 2,800 dd in 2019 and by 2050, to estimate the favourable area for establishment of tick populations and its growth over time. Degree-days were calculated for each municipality by determining the average dds in the area based on observations in 2019 (average: 2015–2019) and based on projections for 2050 (average: 2014–2071) for RCPs 4.5 and 8.5.

The average incidence rates were then calculated in the area favourable to the establishment of ticks (>2,800 dd) and outside that area (<2,800 dd) for the reference year 2019 (year with the highest incidence rate in our study period) as follows: number of cases reported in the area/number of residents in the area. Finally, three incidence rate scenarios were considered to account for the possible evolution by 2050: Scenario 1 (stable incidence rate): the incidence rates remain similar to those calculated in 2019 inside and outside the area favourable to the establishment of ticks; Scenario 2 (higher incidence rate in one region): the incidence rates remain similar to those calculated in 2019, except in the Estrie region, which is the region with the highest incidence rate in 2015–2019; for that region, the incidence rate calculated in that region in 2019 is used; Scenario 3 (high incidence rates): the incidence rate in Estrie calculated in 2019 is applied to all areas favourable to the establishment of ticks by 2050. These incidence rates made it possible to calculate the number of cases expected based on demographic projections for Québec. Finally, the analyses conducted combine two climate scenarios (RCP 4.5 and RCP 8.5), three demographic scenarios (moderate, low and high) and three incidence rate scenarios (stable, higher in one region, high) for a total of 18 scenarios. The direct costs for healthcare expenditures for the 2050 horizon were calculated by correlating the number of cases expected in 2050 to the cost per patient estimated in 2019.

Results

Epidemiology

Incidence rate and demographic characteristics

Between 2015 and 2019, 1,473 cases of Lyme disease were reported in Québec, giving an average incidence rate of 3.58 cases/100,000 inhabitants for the period for the entire province. Men represented 58% of cases reported and the average age is 44 years (range: <1 year–89 years, median: 48 years) (**Table 1**). The distribution by age is bimodal: 0 to 9 years represents 10% of cases and 50 to 69 years represents 39% of cases. Distribution by age group is similar among men and women (p=0.35).

The demographic characteristics are similar for the 6,392 individuals who reported ticks to the passive surveillance program between 2015 and 2019. Of those individuals, 57% were men and the average age was 39 years (range: <1 year to 93 years, median 42 years). The distribution by age is bimodal: 0 to 9 years represents 18% of cases and 50 to 69 years represents 35% of cases. This distribution is similar among men and women (p=0.08).

Likely region of acquisition or exposure

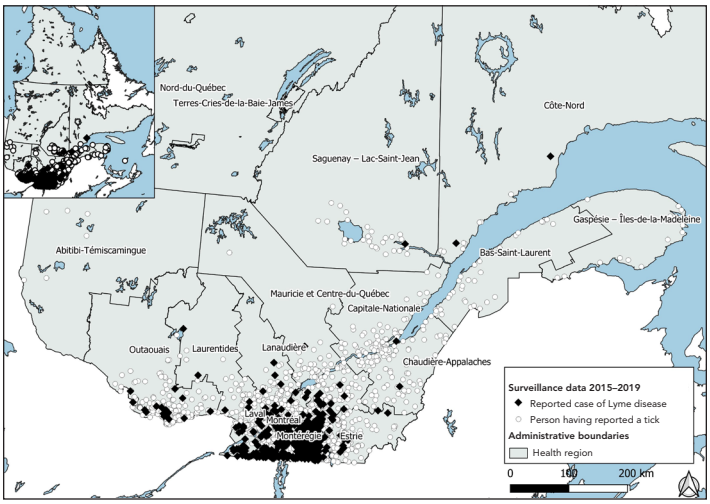
A total of 74% of reported cases acquired their infection in Québec, primarily in the south of the province: 58% in Estrie and 34% in Montérégie (Table 1 and **Figure 1**). The incidence rate is below 6 cases/100,000 inhabitants for all regions of Québec, except Estrie, which averaged 35 cases/100,000 inhabitants for 2015–2019. Despite a large number of cases, the incidence rate in Montérégie is relatively low (5 cases/100,000 inhabitants), mainly due to the size of the region's population. Of the cases acquired outside Québec, 52% were acquired in the United States (state not specified).

The geographic distribution of individuals who reported a tick to the passive surveillance program is larger than that of acquisition of Lyme disease (Figure 1). People reported ticks in all regions of Québec, except Nord-du-Québec. Terres-Cries-de-la-Baie-James and Nunavik. More people reported ticks in southern Québec (29% in Estrie, 23% in Montérégie and 13% in Outaouais).

Table 1: Epidemiological characteristics of cases of Lyme disease reported in Québec, 2015–2019

Reported cases	n	%
Number of cases (n=1,473)		
Acquired in Québec	1,098	74%
Acquired outside Québec	334	23%
Unknown	41	3%
Age group (years) (n=1,473)		
0–9	144	10%
10–19	139	9%
20–29	96	7%
30–39	171	12%
40–49	198	13%
50–59	281	19%
60–69	300	20%
70–79	126	9%
80–89	18	1%
Sex (n=1,469)		
Male	858	58%
Female	611	42%
Likely location of acquisition outside Québec (n=334)		
United States	174	52%
Other province of Canada	94	28%
Europe	49	15%
Other	17	5%
Likely location of acquisition inside Québec (n=1,025)		
Estrie	590	58%
Montérégie	352	34%
Mauricie-et-Centre-du-Québec, Outaouais, Lanaudière, Laurentides, Laval, Montréal	78	8%
Capitale-Nationale, Chaudière-Appalaches, Saguenay–Lac-Saint-Jean, Côte-Nord	5	<1%
Abitibi-Témiscamingue, Gaspésie–Îles-de-la-Madeleine, Bas-Saint-Laurent, Nord-du-Québec	0	0%
Cases acquired in Québec in a known region (n=1,025)		
Acquired in region of residence	875	85%
Region of residence (n=1,473)		
Estrie	548	37%
Montérégie	436	29%
Montréal	229	16%
Mauricie et Centre-du-Québec, Outaouais, Lanaudière, Laurentides, Laval	230	16%
Capitale-Nationale, Chaudière-Appalaches, Saguenay–Lac-Saint-Jean, Bas-Saint-Laurent	21	1%
Abitibi-Témiscamingue, Gaspésie–Îles-de-la-Madeleine, Côte-Nord, Nord du Québec	9	<1%

Figure 1: Likely location of acquisition of reported cases of Lyme disease and exposure of persons who reported a tick, Québec, 2015–2019



Region of residence

The region of residence of the case may be different from the region where the disease was acquired. Between 2015 and 2019, Lyme disease affected residents in all regions of Québec, except Nunavik and Terres-Cries-de-la-Baies-James. Of the reported cases, 37% lived in Estrie, 30% in Montérégie and 16% in Montréal (Table 1). The other regions account for less than 60 cases among their residents.

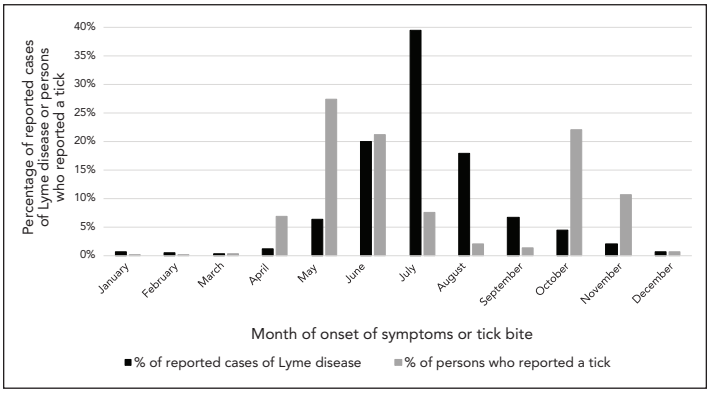
On average, cases acquired in the person's region of residence represent 85% of cases reported and acquired in Québec (59% of all reported cases), but there continue to be significant variations between regions. For Montérégie and Estrie, most cases are acquired in their region of residence (73% and 90% respectively), while that figure is only 1% for Montréal. Most cases reported in Montréal are acquired in another region of Québec (40%, mostly in Estrie and Montérégie) or outside Québec (53%).

Seasonality

Cases of Lyme disease can occur throughout the year. However, in at least three of four cases (77%), the onset of symptoms is between June and August, with a peak in July (39% of cases) (**Figure 2**).

Ticks are also reported to the surveillance program throughout the year, with 60% of people reporting between April and July (peak in May) and 35% between October and November (peak in October) (Figure 2). People mainly reported adult ticks (92% of ticks reported), and 19% of ticks analyzed were infected with *B. burgdorferi*.

Figure 2: Month of onset of symptoms in reported cases of Lyme disease and reported tick bites, Québec, 2015–2019



Clinical characteristics

Reporting of cases

Over the period of 2015–2019, cases were reported on average 60 days after the onset of the first symptoms (median: 36 days; standard deviation: 124 days). Only 32% of cases were reported directly by a physician and not by a laboratory following a diagnostic test (**Table 2**).

Clinical signs and stages

To prepare a clinical portrait of the 1,473 cases, the data provided by the DSPu (n=405 cases) and Musonera *et al.*, (14) (n=272 cases) were used. On average, 66% of cases of Lyme disease are at the localized stage, and 34% at the disseminated stage when reported (Table 2).

For all cases, 65% present typical erythema migrans and 22% multiple erythema. The most commonly cited general symptoms are fatigue (34%), fever (29%), arthralgia (29%), headaches (28%) and myalgia (25%). There were neurological symptoms in 25% of cases, cardiac symptoms in 3% of cases and Lyme arthritis in 11% of cases (Table 2). One person can present multiple symptoms.

Hospitalization

According to data reported by the DSPu and Musonera *et al.*, (14), an average of 7% of reported cases required short-term hospitalization (1–4 days), or 103 cases over our study period.

Evolution and death

The ND indicates recovery (improvement or disappearance of clinical signs) at the time of the epidemiological investigation for 71% of cases and after-effects for 1% of cases. No deaths were reported in the ND for our study period.

Table 2: Clinical characteristics of cases of Lyme disease reported in Québec, 2015–2019

Cases reported 2015–2019	n	%
Time between onset of symptoms and reporting of the case (n=1,329)[a]		
<1 month	609	46%
1–3 months	564	42%
>3 months	156	12%
Case reported (n=1,473)[a]		
By a physician	477	32%
By a laboratory	996	68%
Clinical stages (n=1,473)[a]		
Localized	972	66%
Disseminated	501	34%
Early	398	27%
Late	103	7%
Clinical signs (n=1,473)[b,c]		
General		
Fever	427	29%
Fatigue	501	34%
Headache	412	28%
Cutaneous		
Typical erythema migrans	957	65%
Multiple erythema migrans	324	22%
Acrodermatitis chronica atrophicans	0	0%
Musculoskeletal		
Myalgia	368	25%
Arthralgia	427	29%
Arthritis	162	11%
Neurological		
Stiff neck	162	11%
Facial paralysis	118	8%
Radiculopathy	15	1%
Meningitis	74	5%
Cardiac		
Heart rate disorder	15	1%
Atrioventricular block (AV block)[d]	29	2%
Carditis	15	1%
Evolution at time of investigation (n=1,473)[a]		
Recovery	1 046	71%
After-effects	20	1%
Unknown	407	28%
Hospitalization (n=1,473)[b]		
1–4 days	103	7%

[a] Estimation of the number and percentage based on the register of notifiable diseases (ND) (n=1,473)
[b] Estimation of the percentage based on data available from public health departments (DSPu) (8–11,23,24) and Musonera *et al.* (14,42), and extrapolation to 1,473 cases to estimate the number of cases per stage and clinical sign and the number of hospitalizations
[c] One person can present several symptoms
[d] Atrioventricular blocks (AV blocks): 0.6% of 1st degree AV blocks, 1% 2nd and 3rd degree AV blocks

Cost of initial care and hospitalization

Initial care

For a case at the localized stage, the cost of initial care (consultation and treatment) is estimated at $47 CAN ($31–$63 CAN). For a case at the disseminated stage, that cost is estimated at $443 CAN ($172–$714 CAN depending on the clinical signs). Applied to all cases, initial care costs an average of $182 CAN per case ($979–$284 CAN) (**Table 3**).

For the 1,473 cases reported during the period of 2015–2019, the cost would be $267,541 CAN ($116,440–$418,627 CAN) over 5 years, or $53,508 CAN per year ($23,288–$83,725 CAN). Cases at the disseminated stage represent 34% of cases reported, but 83% of the cost of treating cases (Table 3).

Hospitalization

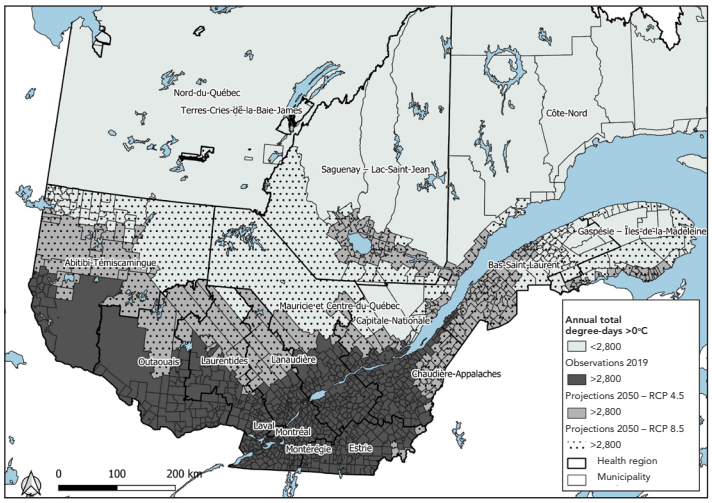
The estimated 103 hospitalizations represent a cost of $589,200 CAN for 2015–2019, or an average of $117,840 CAN/year (Table 3).

Projections for 2050

Québec's population is expected to increase from approximately 8,460,000 in 2019 to approximately 9,550,000 by 2050, an average increase of 13% based on the moderate demographic scenario (low scenario: 8,230,000 inhabitants [-3%], high scenario: 10,8550 000 inhabitants [+28%]) (**Table 4**).

Figure 3 shows that the current climate limits the extent of the area favourable to the establishment of ticks in the southernmost part of Québec. With rising temperatures resulting from increased greenhouse gas emissions, the climate is becoming favourable in almost all inhabited areas in Québec. By 2050, 96% to 98% (RCP 4.5 and 8.5) of Québec's population will live in the climate zone favourable to the establishment of tick populations, compared with 73% in 2019 (Table 4 and Figure 3).

Figure 3: Municipalities located in the climate zone favourable to the establishment of ticks based on the climate scenarios, Québec, 2019 and 2050



Abbreviation: RCP, Representative Concentration Pathway

Table 3: Cost of initial care of reported cases of Lyme disease by clinical stage, Québec, 2015–2019

Québec, 2015–2019	n	Cost per case (CAN$)			Cost 2015–2019 (CAN$)			Cost per year (CAN$)		
		Average	Min	Max	Average	Min	Max	Average	Min	Max
Localized stage	**972; (66%)**	**46.90**	**31.14**	**62.66**	**45,586.80; (17%)**	**30,268.08**	**60,905.52**	**9,117.36**	**6,053,61**	**12,181.10**
General practitioner consultation[a]	972	32.84	19.42	46.25	31,920.48	18,876.24	44,955.00	6,384.10	3,775.25	8,991.00
Doxycycline 200 mg, 1/day, 10–14 days[b]	972	14.07	11.72	16.41	13,676.04	11,391.84	15,950.52	2,735.21	2,278.37	3,190.10
Disseminated stage	**501; (34%)**	**443.17**	**172.08**	**714.25**	**222,028.17; (83%)**	**86,212.08**	**357,839.25**	**44,405.63**	**17,242.41**	**71,567.85**
General practitioner consultation[a]	501	32.84	19.42	46.25	16,452.84	9,729.42	23,171.25	3,290.57	1,945.88	4,634.25
Consultation + specialist follow-up[a]	501	148.76	136.25	161.27	74,528.76	68,261.25	80,796.27	14,905.75	13,652.25	16,159.25
Treatment according to clinical signs[b]	501	261.57	16.41	506.73	131,046.57	8,221.41	253,871.73	26,209.31	1,644.28	50,774.35
Total 2015–2019	**1,473; (100%)**	**181.63**	**79.05**	**284.20**	**267,540.99; (100%)**	**116,440.65**	**418,626.60**	**53,508.19**	**23,288.13**	**83,725.32**
Hospitalization	103; (7%)	2,000.00	1,000.00	4,000.00	206,000.00	103,000.00	412,000.00	41,200.00	20,600.00	82,400.00

Abbreviations: N, number; Min, minimum, Max, maximum
[a] According to the *Régie de l'assurance maladie du Québec* (RAMQ) (25,26)
[b] According to the *Institut national d'excellence en santé et en services sociaux* (INESSS) (27)

Table 4: Number of reported cases of Lyme disease based on the various demographic, climate and incidence rate scenarios, Québec, 2019 and 2050

Scenarios	2019	Emission and demographic scenarios for 2050					
		RCP 4.5			RCP 8.5		
		Moderate	Low	High	Moderate	Low	High
Human population							
Québec	8,460,000	9,550,000	8,230,000	10,850,000	9,550,000	8,230,000	10,850,000
Area dd >2,800	6,187,253	9,177,134	7,908,672	10,426,378	9,350,074	8,057,708	10,622,859
Percentage of Québec population	73%	96%	96%	96%	98%	98%	98%
Incidence scenario[a]							
Scenario 1							
Number of cases acquired in Québec	381	494	426	562	499	430	567
Increase from 2019	+0%	+30%	+12%	+47%	+31%	+13%	+49%
Scenario 2							
Number of cases acquired in Québec	381	693	609	781	698	613	787
Increase from 2019	+0%	+82%	+60%	+105%	+83%	+61%	+107%
Scenario 3							
Number of cases acquired in Québec	381	5,535	4,770	6,289	5,635	4,856	6,403
Increase from 2019	+0%	+1,353%	+1,152%	+1,551%	+1,379%	+1,175%	+1,580%

Abbreviations: dd, degree-days >0ºC; RCP, Representative Concentration Pathway
[a] Incidence scenario: Scenario 1: Incidence rates similar to the moderate rates in 2019, i.e. 5.29 cases/100,000 inhabitants in the area with dd >2,800 and 2.39 in the area with dd <2,800; Scenario 2: incidence rates similar to the moderate rates in 2019 except in Estrie, which maintains its incidence rate from 2019, i.e. 60.22 cases/100,000 inhabitants in Estrie; 5.29 cases/100,000 inhabitants in the area with dd >2,800 and 2.39 in the area with dd <2,800; Scenario 3: incidence rates similar to the Estrie rates in 2019, i.e. 60.22 cases/100,000 inhabitants in the area dd >2,800 and 2.39 in the area dd <2,800

In 2019, the incidence rate in the area favourable to ticks (dd >2,800) is estimated at 5.29 cases/100,000 inhabitants and at 2.39 cases/100,000 inhabitants outside that area (dd <2,800). In scenario 1—with incidence rates similar to those in 2019—projections for 2050 suggest an increase of about 30% in the number of cases acquired in Québec compared with 2019, with the moderate demographic scenario and RCP 4.5, i.e. 494 cases expected compared with 381 in 2019 (426 cases, +12% and 562 cases, +47% for the low and high demographic scenarios). In scenario 2—considering higher incidence rates in the Estrie region, i.e. 60.22 cases/100,000 inhabitants in 2019—the number of cases would almost double compared with 2019, with 693 cases expected for 2015 (609 to 781 cases). In Scenario 3, the entire area favourable to ticks would have an incidence rate similar to that of Estrie, i.e. 60.22 cases/100,000 inhabitants, and the rest of the province would have a rate of 2.39 cases/100,000 inhabitants. By 2050, the number of cases would be 14 times higher than in 2019, with 5,535 cases expected (4,770 to 6,289 cases). For all three scenarios, the projections are relatively similar under RCP 8.5 (Table 4 and Figure 3).

The 494 to 5,535 cases would represent a cost of $88,090 to $1,005,322 CAN by 2050 for initial care. The cost of hospitalization of the 35 to 387 cases would be $140,000 to $1,548,000 CAN. The cost of cases acquired outside Québec (currently 23% of reported cases) would be added to these results.

Discussion

This study describes the current burden of Lyme disease in Québec from an epidemiological, clinical and, in part, economic perspective, based on human and acarological surveillance data from Québec for the period of 2015–2019. It also estimates the number of expected cases by 2050, considering various demographic, climatic and incidence rate scenarios.

The overall incidence rate in Québec is 3.58 cases reported/100,000 inhabitants for the period of 2015–2019. In 2019, Québec had the third highest number cases of Lyme disease among Canadian provinces, behind Ontario and Nova Scotia (43). The incidence rate is higher in the southern parts of Québec, where the disease is endemic, than it is in the other parts of the province, where it is not yet present or is emerging (1,5). The demographic and seasonality characteristics are similar to those for Canada as a whole (43,44), Ontario (45) and Nova Scotia (46).

The epidemiological burden is concentrated in a few regions in southern Québec, where the disease is endemic, but the clinical and economic burden concerns all regions of Québec. Indeed, cases are reported in all regions of Québec and are managed *a priori* by the healthcare system in their region of residence, whether or not the infection was acquired there. In addition, tick exposure is possible in much of the province, even though the majority of exposures are reported in Estrie and Montérégie, two regions where tick populations have been known to be present for over 10 years (1).

Most cases are reported, and thus diagnosed, at the localized stage of the disease. As a result, 65% of reported cases presented erythema migrans, an early symptom of the disease, and only 11% presented Lyme arthritis, the most advanced stage of the disease. Other Canadian studies report a similar proportion of erythema migrans and neurological and cardiac symptoms, but more cases of arthritis (43–47). However, care must be taken in interpreting the results, as access to clinical data is difficult and often limited to the regions most affected by Lyme disease, which limits extrapolation to all of Québec. In addition, the clinical signs of Lyme disease are often not very specific and the stages are hard to determine in practice or from medical records (4,27).

The average cost of initial care is estimated at $182 per patient and varies widely depending on the clinical signs ($47 on average for typical erythema migrans, $443 for carditis). These costs are based on recommendations for the initial treatment of cases (4) and do not consider the extension of treatment in some cases. In Québec, however, clinical evolution is favourable in 99% of serious cases, with objective clinical signs disappearing in less than three months (14,42). In addition, a study conducted in Ontario estimates that most costs occur within 30 days of diagnosis (15). The Canadian Institute for Climate Choices (CICC) (22,48) estimates the long-term cost of Lyme disease (hospitalization, outpatient medical care, medication, treatment and lost productivity) at an average of $26,795 CAN per case in 2016. The authors state that 97% of costs are related to a loss of quality of life and only 0.9% to direct costs of healthcare expenditures, or an average of $241 CAN per case (including hospitalization, medical care and treatment), which is consistent with our study and explains the significant differences between studies of the economic burden of Lyme disease, depending on the costs considered.

Demographic and climate projections suggest 1.3 to 14.5 times more cases acquired in Québec in 2050 than in 2019, with about 500 to 5,500 cases expected by 2050, depending on the incidence rate scenarios. The increased number of cases seems to be related more to the evolution of the incidence rate than the progression of ticks in the area as a result of climate change. In fact, there is little difference between the RCP 4.5 and 8.5 emission scenarios, as human population growth and sprawl are still limited in Québec: the northern parts of the province are sparsely populated, and 80% of the human population lives along the St. Lawrence River or in the regions south of the river (49), which are already areas where Lyme disease is endemic or areas favourable to the establishment of ticks. Nevertheless, the regions will probably not be affected by Lyme disease in the same way. Locally, some municipalities will probably have a higher incidence rate than others, depending on the combination of demographic growth and the increase in tick density in their area. Thus, simply having a region with a higher incidence rate than the rest of the province (Scenario 2) almost doubles the number of cases expected in 2050.

The complexity of the biological models yields different results depending on the parameters chose in the studies (21,22,48,50). The consequences of higher temperatures on the impact of Lyme disease are hard to assess, as the relationship is probably not linear (2,37,50). Other factors will also play a role in the progression of Lyme disease in Québec, such as changes in habitat and the host community favourable to ticks, increased outdoor human activity, urbanization of areas where the disease is endemic, and awareness among the general public of adopting preventive measures (2). Similarly, the evolution of cases acquired outside Québec remains difficult to estimate. Beyond the expected number of cases, it is the general trend that must be considered in adaptation plans, with an increase in the number of cases and geographic distribution, thus impacting regions and human populations that are not yet affected much by the disease.

Limitations

There are several limitations to surveillance data on Lyme disease. First, the number of cases reported or diagnosed does not represent the actual number of cases of Lyme disease (51), which has an impact on the estimation of the burden and related projections. Similarly, the number of people who reported a tick to Québec's passive surveillance system underestimates the actual number of people bitten by a tick (51).

The clinical burden is based on epidemiological investigations conducted in regions where Lyme disease has been endemic for several years, which may limit the validity of their extrapolation to other regions of Québec. More detailed clinical studies of all cases of Lyme disease in Québec would be needed to refine the clinical picture.

The economic estimate presented in this study does not take into account all costs associated with Lyme disease. For example, some costs, such as absenteeism from work, reduced quality of life, the cost of laboratory tests, post-exposure prophylaxis or disease surveillance, were not considered but contribute to the total burden of Lyme disease in Québec.

Conclusion

This study provides an initial portrait of the burden of Lyme disease in Québec. Although the cases are acquired primarily in the southern part of the province, all of Québec is already concerned about the management of Lyme disease. The results present an order of magnitude of the current and future burden of Lyme disease, how to prepare the regions of Québec to adapt and optimize public health protection measures.

Authors' statement

MR — Conceptualization, collecting and managing data, data analysis, data interpretation, writing–original draft, writing–revision and editing, final approval
AI-C, AA-P, NO — Conceptualization, writing–revision and editing, final approval
GB, CB, AC, FM, PAP, KT, KZ, — Conceptualization, editing, final approval
DC — Writing-revision and editing, final approval

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Competing interests

None.

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