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CANADA COMMUNICABLE DISEASE REPORT

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The cover photo represents a group of diverse people showing plasters after vaccination. The image was taken from Adobe Stock #459705147.

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INFLUENZA VACCINATION

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Summary of the National Advisory Committee on Immunization (NACI) Seasonal Influenza Vaccine Statement for 2024–2025

Anabel Gil[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 2024–2025* updates the NACI recommendations from the previous year.

Objective: To summarize the 2024–2025 NACI seasonal influenza vaccine recommendations and to highlight new and updated information.

Methods: For the development of the *Statement on Seasonal Influenza Vaccine for 2024–2025*, the NACI Influenza Working Group applied the NACI evidence-based process to assess available evidence and formulate recommendations. These recommendations underwent a thorough evaluation and were approved by NACI based on the available evidence.

Results: Key updates for the 2024–2025 influenza season include updated immunization recommendations reflecting changes in influenza epidemiology and revised guidance for vaccine administration during pregnancy and in older adults.

Conclusion: The National Advisory Committee on Immunization recommends that any age-appropriate quadrivalent or trivalent influenza vaccine should be used for individuals six months of age and older who do not have contraindications or precautions. NACI reaffirms the importance of influenza vaccination with inactivated or recombinant influenza vaccines in pregnancy. Finally, NACI recommends that inactivated high-dose (IIV-HD), inactivated adjuvanted (IIV-Adj) or recombinant influenza vaccine (RIV) should be offered, when available, over other influenza vaccines for adults 65 years of age and older.

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Introduction

Each year, Canada experiences seasonal influenza epidemics, primarily during late fall and winter. The severity of these outbreaks fluctuates annually due to factors such as circulating virus types and affected populations (1). On average, Canada sees approximately 12,200 influenza-related hospitalizations and 3,500 influenza-related deaths annually (2,3). Vaccination remains the most effective defence against influenza and its complications.

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with annual recommendations on the use of authorized seasonal influenza vaccines, reflecting shifts in epidemiology, immunization practices and available products in Canada. The NACI Influenza Working Group leads the annual update of the NACI Statement on Seasonal Influenza Vaccine, involving a thorough review and evaluation of the literature as well as discussion and debate

at the scientific and clinical practice levels. On July 25, 2024, PHAC released new guidance from NACI on the use of seasonal influenza vaccines for the 2024–2025 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 2024–2025 influenza season, with emphasis on new or updated information since the *Statement on Seasonal Influenza Vaccine for 2023–2024*. Conclusions from evidence reviews on the use of influenza vaccine during pregnancy and in older adults are also presented. Additionally, the article addresses ongoing research following recent outbreaks of highly pathogenic avian influenza (HPAI) A(H5N1). For detailed information, refer to the new *NACI Advisory Committee Statement on Seasonal Influenza Vaccine for 2024–2025* (the Statement) on the PHAC website (4).

Methods

In the preparation of the 2024–2025 seasonal influenza vaccine recommendations, NACI's Influenza Working Group identified the need for evidence reviews for new topics, analyzed available evidence and developed updated recommendations using NACI's evidence-based process. 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 (5).

The 2024–2025 Statement includes an addendum (6) with updated guidance on influenza immunization in response to the global absence of B/Yamagata viruses. Recommendations and supporting evidence from 1) *Updated Guidance on Influenza Vaccination During Pregnancy* (7) and 2) *Supplemental Guidance on Influenza Vaccination in Adults 65 Years of Age and Older* (8), both published since the 2023–2024 Statement, were also integrated.

For more information on NACI recommendations related to seasonal influenza vaccination, please see the Canadian Immunization Guide chapter on influenza vaccines (9), as well as additional statements on the NACI web page.

Results

New or updated information for 2024–2025

Addendum to the 2024–2025 Statement: The 2024–2025 Statement includes an addendum with updated information and guidance on influenza vaccines, reflecting the global absence of B/Yamagata viruses since March 2020. NACI supports transitioning from quadrivalent to trivalent influenza vaccines based on this change in epidemiology, the theoretical risk of reintroduction of B/Yamagata viruses with the continued production and use of quadrivalent vaccines, and World Health Organization (WHO) recommendations and expert consensus. Therefore, NACI has removed its preferential recommendation for quadrivalent vaccines in children, and now, **NACI recommends that any age-appropriate quadrivalent or trivalent influenza vaccine should be used for individuals six months of age and older who do not have contraindications or precautions.** For the 2024–2025 influenza season in Canada, vaccine availability is anticipated to remain unchanged, with quadrivalent formulations continuing to be supplied for public programs. Adjuvanted inactivated influenza vaccines will remain trivalent and continue to be available in Canada. Please refer to the *Addendum to the NACI Statement on Seasonal Influenza Vaccine for 2024–2025 – Transition from Quadrivalent to Trivalent Influenza Vaccines* for more information (6).

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

- The use of influenza vaccines during pregnancy: NACI continues to **strongly recommend that inactivated or recombinant influenza vaccines be offered during pregnancy, at any gestational age.** NACI also continues to include pregnant individuals among those for whom influenza vaccination is particularly important. Finally, NACI reaffirms its recommendation that influenza vaccination may be given at the same time as, or at any time before or after administration of another vaccine, including the COVID-19 or pertussis vaccine.
  For complete details of this review, rationale, relevant considerations and additional information supporting this recommendation, refer to the *Updated Guidance on Influenza Vaccination During Pregnancy* (7).
- The use of influenza vaccines in older adults: NACI strongly recommends that **inactivated high-dose (IIV-HD), inactivated adjuvanted (IIV-Adj) or recombinant influenza vaccine (RIV) should be offered, when available, over other influenza vaccines for adults 65 years of age and older.** If a preferred product is not available, any of the available age-appropriate influenza vaccines should be used.
  For complete details of this review, rationale, relevant considerations and additional information supporting this recommendation, refer to the *Supplemental Guidance on Influenza Vaccination in Adults 65 Years of Age and Older* (8).

Seasonal influenza guidance in the context of highly pathogenic avian influenza (HPAI) A(H5N1) outbreaks: Due to recent HPAI A(H5N1) outbreaks in poultry and mammals, including, as of July 2024, multiple cases in the United States of bird-to-human and cow-to-human transmissions, NACI reiterates its recommendation that all individuals six months of age and older should receive a seasonal influenza

vaccine. This includes those likely to have significant risk of exposure to influenza A(H5N1) through interactions with birds or mammals (such as poultry, livestock, slaughterhouse and processing plant workers, wildlife officers/researchers and veterinarians). NACI will be conducting an evidence review to determine if there is a need to permanently expand its list of individuals for whom influenza vaccination is particularly important, beyond the current group, to others at high risk of exposure to circulating A(H5N1) viruses.

More information can be found in the *Important notice 2: Outbreaks of highly pathogenic avian influenza in Canada and U.S.* section of the *Seasonal Influenza Vaccine for 2024–2025* on the PHAC website (4).

Summary of National Advisory Committee on Immunization recommendations for the use of influenza vaccines for the 2024–2025 influenza season

The National Advisory Committee on Immunization recommends that any age-appropriate quadrivalent or trivalent influenza vaccine should be used for individuals six months of age and older who do not have contraindications or precautions. 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**:

- Both quadrivalent and trivalent formulations are clinically safe and effective
- Since March 2020, B/Yamagata viruses have not been detected globally, leading to the recommendation to exclude the B/Yamagata component from 2024 to 2025 influenza vaccines, aligning with WHO guidance
- Previously, quadrivalent vaccines were preferred for children due to the presence of both influenza B components, and NACI now has no preference between quadrivalent and trivalent vaccines

List 1: Groups for whom influenza vaccination is particularly important[a]

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[b]:
  - Cardiac or pulmonary disorders (including 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 neurodevelopmental 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)[c]
  - Morbid obesity (defined as BMI of 40 kg/m² 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 syndrome associated with influenza
- All individuals who are pregnant
- All individuals 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 younger 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 newborn to 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] List reproduced from *NACI Seasonal Influenza Vaccine Statement for 2024–2025* (4)
[b] Refer to *Immunization of Persons with Chronic Diseases* (10) and *Immunization of Immunocompromised Persons* (11) in Part 3 of the Canadian Immunization Guide for additional information about vaccination of people with chronic diseases
[c] Refer to the *NACI Statement on Seasonal Influenza Vaccine for 2018–2019* (12) for rationale supporting the decision to include persons with neurologic or neurodevelopment conditions among the groups for whom influenza vaccination is particularly important and the *Literature Review on Individuals with Neurologic or Neurodevelopment Conditions and Risk of Serious Influenza-Related Complications* (13) for additional details of the evidence reviews that were conducted

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

- Children aged six to 23 months can receive IIV-Adj, standard-dose inactivated influenza vaccine (IIV-SD) and mammalian cell culture based inactivated influenza vaccine (IIV-cc).
  - Influvac Tetra (IIV4-SD) is not recommended for those younger than three years due to insufficient evidence.
- Children six to 17 years can receive IIV-SD, IIV-cc and live attenuated influenza vaccine (LAIV).
  - LAIV is suitable for children with stable, non-severe asthma, cystic fibrosis (without immunosuppressive drug treatment) and stable HIV infection (if being treated with antiretroviral therapy and has adequate immune function).
  - LAIV should not be used in children or adolescents with contraindications or precautions, including severe asthma, medically attended wheezing within the past seven days, current receipt of aspirin or aspirin-containing therapy and immune compromising conditions. Stable HIV infection is an exception, provided the child has been on highly active antiretroviral therapy for at least four months with adequate immune function. Live attenuated influenza vaccine should also not be used in pregnancy; IIV-SD or IIV-cc are preferred choices during pregnancy.
  - IIV4-SD is not recommended for those younger than three years due to insufficient evidence.
- Adults 18 to 59 years can receive IIV-SD, IIV-cc, RIV and LAIV; however, inactivated influenza vaccine may provide better protection than LAIV in healthy adults.
  - LAIV is not recommended for adults with any chronic health conditions listed in List 1 (including immune compromising conditions) and healthcare workers. LAIV is also not recommended in pregnancy; IIV-SD, IIV-cc or RIV are preferred choices during pregnancy.
- Adults 60 to 64 years can receive IIV-SD, IIV-cc and RIV.
- Adults 65 years of age and older should preferentially receive IIV-HD, IIV-Adj or RIV, when available, over IIV-SD and IIV-cc. If a preferred product is not available, any age-appropriate influenza vaccine should be used.

For more information, refer to the *Addendum to the NACI Statement on Seasonal Influenza Vaccine for 2024–2025 – Transition from Quadrivalent to Trivalent Influenza Vaccines* (6). The Canadian Immunization Guide Chapter on Influenza Vaccines has also been updated accordingly.

Recommended dose and route of administration of influenza vaccine types by age, are summarized in **Table 1**.

Table 1: Recommended dose and route of administration, by age, for influenza vaccine types authorized for the 2024–2025 influenza season[a]

Age group	Influenza vaccine type (route of administration)						Number of doses required
	IIV-SD[b] (IM)	IIV-cc[c] (IM)	IIV-Adj[d] (IM)	IIV-HD[e] (IM)	RIV[f] (IM)	LAIV[g] (intranasal)	
6–23 months[h]	0.5 mL[i]	0.5 mL	0.25 mL	-	-	-	1 or 2[j]
2–8 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1 or 2[j]
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: IIV-Adj, adjuvanted inactivated influenza vaccine; IIV-cc, mammalian cell culture based inactivated influenza vaccine; IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard-dose inactivated influenza vaccine; IM, intramuscular; LAIV, live attenuated influenza vaccine; RIV, recombinant influenza vaccine

[a] Table reproduced from *National Advisory Committee on Immunization Seasonal Influenza Vaccine Statement for 2024–2025* (4)
[b] Afluria® Tetra (five years and older), Flulaval® Tetra (six months and older), Fluzone® Quadrivalent (six months and older), Influvac® Tetra (three years and older)
[c] Flucelvax® Quad (six months and older)
[d] Fluad Pediatric® (6–23 months) or Fluad® (65 years and older)
[e] Fluzone® High-Dose Quadrivalent (65 years and older)
[f] Supemtek™ (18 years and older)
[g] FluMist® Quadrivalent (2–59 years)
[h] There is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than three years of age
[i] 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. 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* (14)
[j] 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

Conclusion

The National Advisory Committee on Immunization 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 2024–2025 influenza season, NACI: 1) recommends that any age-appropriate quadrivalent or trivalent influenza vaccine should be used for individuals six months of age and older who do not have contraindications or precautions; 2) continues to strongly recommend that inactivated or recombinant influenza vaccines be offered during pregnancy, at any gestational age; and 3) strongly recommends that IIV-HD, IIV-Adj or RIV should be offered, when available, over other influenza vaccines for adults 65 years of age and older.

Authors' statement

AG — Writing–original draft, writing–review & editing
WS — Writing–review & editing
JP — Writing–review & editing

The *NACI Seasonal Influenza Vaccine Statement for 2024–2025* was prepared by N Sicard, A Sinilaite, W Siu, P Doyon-Plourde 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, Enanta 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

Summary of the National Advisory Committee on Immunization (NACI) Supplemental Guidance on Influenza Vaccination in Adults 65 Years of Age and Older

Pamela Doyon-Plourde[1], Angela Sinilaite[1], Jesse Papenburg[2,3,4,5] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Adults 65 years of age and older are at higher risk of influenza complications, such as hospitalization and death. As a result, seasonal influenza immunization is particularly important for this group.

Objective: This supplemental statement provides an evidence summary on the preferential use of one or more of the age-appropriate influenza vaccines for adults 65 years of age and older, over other age-appropriate influenza vaccines.

Methods: The National Advisory Committee on Immunization (NACI)'s Influenza Working Group undertook an overview of existing systematic reviews on the efficacy, effectiveness, safety and cost effectiveness of influenza vaccination in adults 65 years of age and older. Additionally, NACI's evidence-based process was used to assess the quality of eligible studies, summarize and analyze the findings and apply an ethics, feasibility and acceptability lens to develop recommendations.

Results: The evidence suggests that high-dose inactivated influenza vaccine (IIV-HD), adjuvanted inactivated influenza vaccine (IIV-Adj) and recombinant influenza vaccine (RIV) offer increased benefits for adults 65 years of age and older when compared to standard dose influenza vaccines. The IIV-HD had the most supporting evidence, followed by IIV-Adj and then RIV. Evidence comparing these enhanced vaccines was limited.

Conclusion: Following a thorough review of the complete body of evidence, NACI recommends that IIV-HD, IIV-Adj or RIV should be offered over other influenza vaccines for adults 65 years of age and older. NACI also continues to strongly recommend the inclusion of adults 65 years of age and older among those for whom it is particularly important to receive influenza vaccination.

Suggested citation: Doyon-Plourde P, Sinilaite A, Papenburg J, on behalf of the National Advisory Committee on Immunization (NACI). Summary of the National Advisory Committee on Immunization (NACI) Supplemental Guidance on Influenza Vaccination in Adults 65 Years of Age and Older. Can Commun Dis Rep. Can Commun Dis Rep 2024;50(11):387–92. https://doi.org/10.14745/ccdr.v50i11a02

Keywords: NACI, National Advisory Committee on Immunization, guidance, influenza, influenza vaccine, older adults

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Introduction

Adults 65 years of age and older are at higher risk of severe influenza infection and related complications such as pneumonia, hospitalization and death. This risk is significantly higher with increasing age, presence and severity of chronic medical conditions and higher levels of frailty (1–4). Considering the burden of disease in this population, the National Advisory Committee on Immunization (NACI) has identified adults 65 years of age and older as one of the groups at higher risk of influenza complications for whom influenza immunization is particularly important (***Strong NACI Recommendation***) (5).

NACI has conducted several reviews over the years to evaluate the best available scientific and clinical evidence to develop recommendations for the use of influenza vaccines, with a focus on optimizing influenza protection among older adults in Canada (6,7).

Other than a recommendation for using high-dose inactivated influenza vaccines (IIV-HD) over standard-dose inactivated influenza vaccine (IIV-SD) formulations, NACI has not previously made comparative individual-level recommendations on the use of other available vaccines in this age group. On a public health program level, NACI has recommended that any of the available influenza vaccines authorized in this age group should be used, as there was insufficient evidence on the incremental value of different influenza vaccines to make comparative public health program-level recommendations on the use of available vaccines.

Given the expressed desire by provincial and territorial programs for guidance on optimal product choice(s) for older adults, NACI has undertaken a review of evidence to determine whether any one or more of the age-appropriate influenza vaccines for adults 65 years of age and older should be preferentially used over other age-appropriate influenza vaccines. A systematic review of economic literature was also undertaken to inform public health program decision-making.

Table 1: Population, intervention, comparator(s), outcome(s) criteria guiding National Advisory Committee on Immunization's evidence review[a]

PICO	Criteria
Population	Adults 65 years of age and older
Intervention	Inactivated influenza vaccine (IIV)-not standard (not-SD) and recombinant influenza vaccines: • High-dose inactivated influenza vaccine (IIV-HD) • MF-59 adjuvanted inactivated influenza vaccine (IIV-Adj) • Recombinant influenza vaccine (RIV) • Mammalian cell culture-based vaccine (IIV-cc)
Comparator	Inactivated standard-dose influenza vaccines (IIV-SD), inactivated influenza vaccine (IIV)-not SD and RIVs
Outcomes[b]	Vaccine efficacy/effectiveness: • Lab-confirmed influenza (LCI) • Influenza-associated outpatient/emergency department (ED) visits (LCI, influenza-like illness [ILI]) • Influenza-associated hospitalization (LCI, ILI) • Influenza-associated vascular events Vaccine safety: • Any solicited systemic adverse reaction grade ≥3 • Guillain-Barré Syndrome (GBS) • Any serious adverse event (SAE) • Any solicited injection site adverse reaction grade ≥3 Economics: • Vaccine cost effectiveness (cost per life year saved, cost per influenza case averted) • Cost-utility (cost per quality-adjusted life year [QALY])

Abbreviations: ED, emergency department; GBS, Guillain-Barré Syndrome; IIV, inactivated influenza vaccine; IIV-Adj, adjuvanted inactivated influenza vaccine; IIV-cc, mammalian cell culture-based inactivated influenza vaccine; IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard-dose inactivated influenza vaccine; ILI, influenza-like illness; LCI, laboratory-confirmed influenza; PICO, population, intervention, comparator and outcomes framework; QALY, quality-adjusted life year; RIV, recombinant influenza vaccine; SAE, serious adverse event
[a] Table adapted from *NACI Supplemental guidance on influenza vaccination in adults 65 years of age and older* (8)
[b] Critical/important outcomes for decision-making

Methods

The NACI Influenza Working Group undertook an overview of existing systematic reviews to answer the following research question: Should any age-appropriate influenza vaccine(s) be preferentially used in adults 65 years of age and older? The literature search and data extraction were conducted according to the following population, intervention, comparator and outcomes (PICO) framework (**Table 1**).

The GRADE-ADOLOPMENT process was employed to adapt recommendations from the United States Advisory Committee on Immunization Practices guideline panel where they assessed the relative benefits and harms of IIV-HD, adjuvanted inactivated influenza vaccines (IIV-Adj) and recombinant influenza vaccine (RIV) compared to one another and with IIV-SD in adults 65 years of age and older (9,10). Evidence synthesis on the efficacy and cost effectiveness of influenza vaccines in adults 65 years of age and older was further expanded with two additional systematic reviews, both developed in collaboration with the Methods and Applications Groups for Indirect Comparisons through the Drug Safety and Effectiveness Network and supervised by the NACI Influenza Working Group. One review examined the efficacy of influenza vaccines in older adults, while the second review delved into the cost effectiveness of seasonal influenza vaccines in older adults. Further details regarding the methodologies employed in both Drug Safety and Effectiveness Network reviews were published in pre-specified protocols (11,12).

To support this work, a systematic assessment of ethics, equity, feasibility and acceptability of influenza vaccine guidance was conducted according to established NACI methods (13). The NACI evidence-based process was used to assess the available evidence and develop updated recommendations (14). Details and results can be found in the *NACI supplemental guidance on influenza vaccination in adults 65 years of age and older* (8).

Results

NACI's evidence base encompassed an overview of three systematic reviews and meta-analyses to determine if certain authorized age-appropriate influenza vaccines are better suited for adults 65 years of age and older compared to others, analyzing findings from a total of 57 unique primary studies (10,15,16). Based on the available evidence, NACI concluded that IIV-HD, IIV-Adj and RIV offer greater benefits when compared to IIV-SD, while maintaining the same level of safety (**Table 2**). Additionally, IIV-HD and IIV-Adj also appear to be cost-effective. Of note, no evidence identified in this review compared mammalian cell culture-based inactivated influenza vaccine (IIV-cc) to other influenza vaccines. Following its thorough review, NACI issued a new recommendation on influenza vaccination in adults 65 years of age and older.

Recommendation

NACI recommends that IIV-HD, IIV-Adj or RIV should be offered over other influenza vaccines for adults 65 years of age and older. If a preferred product is not available, any of the available age-appropriate influenza vaccine should be used. (*Strong NACI Recommendation*)

- Where supply of IIV-HD, IIV-Adj or RIV is limited, consideration can be given to prioritizing groups at highest risk of severe outcomes from influenza among adults 65 years of age and older, such as advanced-age older adults (e.g., 75 years of age and older), those with one or more comorbidities, older frail adults and residents of nursing homes and other chronic care facilities.

Table 2: Comparison of the characteristics of influenza vaccine types available for use in adults 65 years of age and older[a]

Characteristics	IIV-HD, IIV-Adj and RIV compared to IIV-SD
Efficacy and effectiveness	IIV-HD, IIV-Adj and RIV appear to have increased vaccine efficacy and effectiveness as compared to IIV-SD. Notably, IIV-HD has the most substantial body of supporting evidence, followed by IIV-Adj and then RIV. The magnitude of relative benefit varied and was not seen in all studies and all seasons. There are few RCTs comparing IIV-HD, IIV-Adj and RIV to IIV-SD and to one another. No RCT compared IIV-Adj with IIV-SD for the outcome of LCI. No definitive conclusion can be reached regarding the superiority of any of these vaccines over one another as there is limited evidence directly comparing IIV-HD, IIV-Adj and RIV against each other. There is limited evidence on newer vaccine technologies (e.g., IIV-cc and RIV). Further evidence is needed on the efficacy and effectiveness of influenza vaccines in subpopulations of adults 65 years of age and older at higher risk of severe influenza-related outcomes and complications, such as advanced-age older adults, individuals living with one or more chronic medical conditions and frail individuals.
Safety	IIV-HD, IIV-Adj and RIV appear to be well-tolerated and safe alternatives to IIV-SD in adults 65 years of age and older. Evidence suggests that there is no difference in safety between IIV-HD, IIV-Adj and RIV based on direct evidence among adults 65 years of age and older. Only a few studies reported data for certain vaccine comparisons (e.g., IIV-Adj vs RIV4). Limited data were available for Guillain-Barré Syndrome.
Economics	IIV-HD and IIV-Adj may be considered cost-effective when compared to IIV-SD under commonly used cost-effectiveness thresholds (17). There is no economic evidence directly comparing IIV-HD, IIV-Adj, and RIV against each other (16).
Ethics, equity, feasibility and acceptability	Equity could potentially be increased for older adults at greater risk of severe illness and influenza-related complications if they are given vaccines with higher efficacy. Feasibility from a provider and policymaker perspective may be decreased as enhanced vaccines have higher costs and the level of increased efficacy is uncertain. Acceptability may be increased for high-risk groups due to increased perceived benefits of preferred vaccines in adults 65 years of age and older. Reducing the burden of disease may increase acceptability from the providers' and policymakers' perspectives; however, due to a lack of data supporting higher efficacy and potential increased costs, the use of a preferred vaccine may not be as acceptable.

Abbreviations: IIV-Adj, adjuvanted inactivates influenza vaccines; IIV-HD, high-dose inactivated influenza vaccines; IIV-SD, standard-dose inactivated influenza vaccines; LCI, laboratory-confirmed influenza; RCT, randomized controlled trial; RIV, recombinant influenza vaccine; RIV4, recombinant quadrivalent influenza vaccine

[a] Table taken from *NACI Statement on Seasonal Influenza Vaccine for 2024–2025* (5)

Summary of evidence

- IIV-HD, IIV-Adj and RIV appear to have increased vaccine efficacy/effectiveness as compared to IIV-SD.
- No definitive conclusion can be reached regarding the superiority of any of these vaccines over one another as there is a limited number of studies directly comparing IIV-HD, IIV-Adj and RIV against each other. Notably, IIV-HD has the most substantial body of supporting evidence, followed by IIV-Adj and then RIV.
- IIV-HD, IIV-Adj and RIV are effective alternatives to IIV-SD, with no identified difference in safety, based on direct evidence among adults 65 years of age and older.
- IIV-HD and IIV-Adj are cost-effective when compared to IIV-SD.

A complete review of evidence and full NACI recommendations are published in the new *NACI Supplemental guidance on influenza vaccination in adults 65 years of age and older* (8). This supplemental guidance aligns with NACI's overarching recommendation for influenza vaccination, available in the *NACI Seasonal Influenza Vaccine Statement*, which is that an age-appropriate influenza vaccine should be offered annually to anyone six months of age and older, noting product-specific contraindications **(*Strong NACI Recommendation*)** (5).

Conclusion

The available evidence suggests potential advantages associated with IIV-HD, IIV-Adj and RIV compared to IIV-SD; however, the available evidence directly comparing these vaccines to one another is insufficient to establish with certainty that one vaccine consistently outperforms the others. Moreover, data for IIV-HD, IIV-Adj and RIV against IIV-SD demonstrated a comparable safety profile. As the body of evidence exploring whether certain authorized age-appropriate influenza vaccines are better suited for adults 65 years of age and older compared to others continues to grow, NACI will continue to monitor the evolving evidence and will update this guidance as needed. Further evaluation of safety, efficacy and effectiveness data for newer vaccine technologies (e.g., IIV-cc and RIV) as well as vaccine comparisons (pairwise or comparisons between multiple vaccines) between newer influenza vaccines among adults 65 years of age and older are encouraged. Other new and emerging research priorities identified include further evaluation of vaccine efficacy and effectiveness of influenza vaccines stratified by subpopulations of adults 65 years of age and older (e.g., health and frailty status); national-level influenza surveillance data among older adults in Canada; timing of influenza vaccination with respect to duration or waning of protection in adults 65 years of age and older; incorporation and investigation of the impact of community immunity, frailty and longer-term functional outcomes on cost effectiveness; and factors that influence vaccine confidence and acceptability among adults 65 years of age and older in Canada.

Authors' statement

PDP — Writing–original draft, writing–review & editing
AS — Writing–review & editing
JP — Writing–review & editing

The *NACI Supplemental guidance on influenza vaccination in adults 65 years of age and older* was prepared by P Doyon-Plourde, A Gil, A Sinilaite, W Siu and J Papenburg, on behalf of the NACI Influenza Working Group and was approved by NACI.

Competing interests

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National Influenza Annual Report 2023–2024: A focus on influenza B and public health implications

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Abstract

The 2023–2024 influenza epidemic saw the return of typical late-season influenza B circulation. The epidemic was declared in week 45 (week ending November 11, 2023) due to the predominant circulation of influenza A(H1N1) and peaked in week 52 (week ending December 30, 2023); however, as influenza A circulation decreased, influenza B detections and the percentage of tests positive increased, reaching its peak in week 14 (week ending April 6, 2024). Influenza B/Victoria dominated this wave of activity, contributing to the ongoing discussion about the apparent disappearance of influenza B/Yamagata. With the recommendation for the removal of influenza B/Yamagata lineages from the recommended seasonal influenza vaccine components, the influenza surveillance community is preparing for the possibility of a new seasonal pattern dominated by influenza B/Victoria circulation. This season, as a result of influenza B/Victoria's overwhelming predominance, younger age groups were primarily affected by the wave of influenza B activity. Over the course of the season, among all influenza B detections, 52% occurred in children aged 0–19 years. Among all influenza B-associated hospitalizations, 46.4% were in children aged 0–19 years, and the highest cumulative hospitalization rates for influenza B were among children younger than five years (n=37 per 100,000 population) and children between the ages of 5–19 years (n=15 per 100,000 population). Continued vigilance and surveillance around influenza B trends and epidemiology is required to contribute to effective epidemic preparedness.

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Introduction

The COVID-19 pandemic has reshaped the global landscape of influenza surveillance, disrupting long-standing seasonal trends while presenting public health authorities with new challenges. Following the 2020–2021 season, which saw no nationally declared influenza epidemic, the 2021–2022 season was marked by a late and brief spring epidemic, reflecting the unpredictable nature of viral patterns. The 2022–2023 season, against the backdrop of a concerning "tripledemic" (1), is when Canada experienced its first fall epidemic since the 2019–2020 season. Continuing this trend, the first half of the 2023–2024 season saw classic influenza A circulation, but was marked by the return of typical late-season influenza B circulation for the first time since the onset of the pandemic, highlighting persistent shifts in influenza dynamics. Influenza B circulation has been the subject of its own shifting landscape, predating the pandemic itself. In pre-pandemic seasons, influenza B lineage dominance often alternated from one season to another with no apparent pattern, switching between B/Victoria to B/Yamagata. The dominant influenza B strain in the 2023–2024 season was influenza B/Victoria, as it has been since the 2018–2019 season.

This surveillance report summarizes the trends observed during the 2023–2024 influenza season in Canada, with a focus on the trends and implications surrounding the return of influenza B/Victoria circulation. For a more fulsome analysis of the 2023–2024 season, please refer to the week 34 FluWatch report (2).

Methods

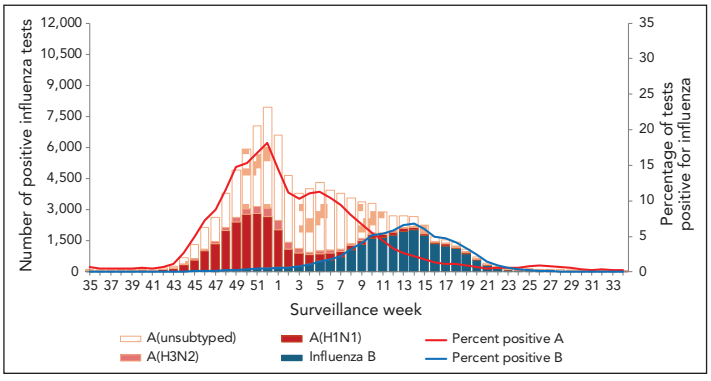
FluWatch is Canada's long-standing influenza surveillance system, which monitors the spread of influenza and influenza-like illness through core surveillance indicators based on global epidemiological standards. FluWatch is a composite surveillance system that consists of seven key areas: virological surveillance; geographic spread; syndromic surveillance; severe outcome surveillance; outbreak surveillance; influenza strain characterization; and vaccination monitoring. Annually, influenza surveillance is conducted across Canada from epidemiological week 35 to week 34 of the following year. For the 2023–2024 Canadian influenza season, this surveillance period began on August 27, 2023, and ended on August 24, 2024. Detailed methods, including surveillance indicator definitions, data sources and statistical analyses can be found on the Public Health Agency of Canada's FluWatch website (3).

Results

Laboratory detections

The 2023–2024 influenza epidemic in Canada began in week 45 (week ending November 11, 2023), when the national percentage of tests positive for influenza exceeded the 5% seasonal threshold (5.07%, 1,344 detections) (4). At the beginning of the epidemic, the majority of influenza detections were influenza A with influenza A(H1N1) being the dominant subtype. The epidemic peaked in week 52 (week ending December 30, 2023) at 18.7% of tests positive for influenza. At this point in the season, influenza A was still the dominant type detected. Following this eight-week period of increase (weeks 45–52), the percentage of tests positive for influenza A began to decrease, concurrently with the increase in the percentage of tests positive for influenza B in week 52. Influenza B reached its peak in week 14 (week ending April 6, 2024) at 6.8% tests positive and was the dominant type detected from weeks 11 to 22. This season, there were 103,173 influenza detections reported, of which 23% (n=23,233) were influenza B. These trends are summarized in **Figure 1**.

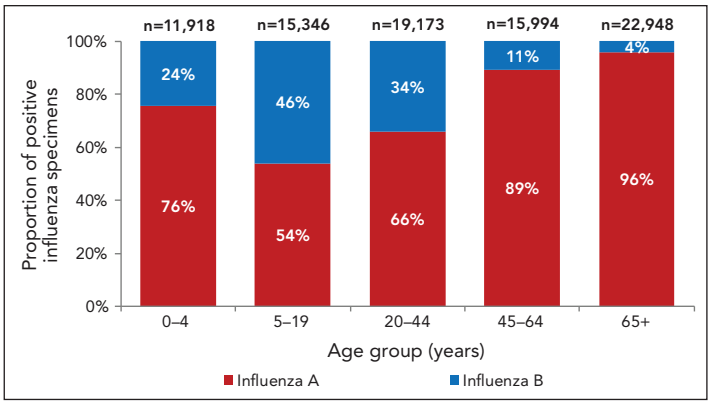
Figure 1: Number of positive influenza tests by type and subtype and percentage of tests positive, by report week, Canada, season 2023–2024



Age distribution of detections

During the 2023–2024 season, in keeping with historical trends, influenza B primarily affected younger age groups. Among all influenza infections in adults aged 65 years and older, only 4% were due to influenza B. Among those aged 45 to 64 years, only 11% of cases were due to influenza B; however, among younger age groups, a much higher proportion of total influenza detections were due to influenza B. For instance, among children aged 0–4 years, 5–19 years and 20–44 years, 24%, 46%, and 34% of detections, respectively, were due to influenza B (**Figure 2**).

Figure 2: Proportion of positive influenza specimens by type and age-group reported through case-based laboratory reporting, Canada, season 2023–2024

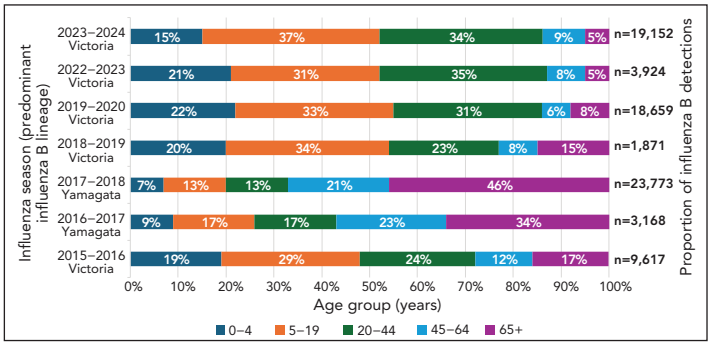


The 2023–2024 season was marked by the return of pre-pandemic influenza B circulation. **Figure 3** compares the age distribution of influenza B detections with accompanying age information from the current season back to the 2015–2016 season. Although in seasons 2015–2016 to 2019–2020, both B/Yamagata and B/Victoria circulated concurrently, for those seasons where B/Victoria was the dominant influenza B type, a greater proportion of detections were reported in individuals younger than 19 years (Figure 3). Conversely in seasons where B/Yamagata was the dominant influenza B type, the majority of detections occurred in older adults, aged 45 to 64 years and 65 years and older. From the seasons 2021–2022 onwards, there has been no detections of circulating B/Yamagata in Canada or abroad (5). Over the course of the 2023–2024 influenza B/Victoria season, among all influenza B detections, more than half (52%) occurred in children aged zero to 19 years. Influenza B/Yamagata and influenza B/Victoria both seem to affect those aged 20 to 44 years; however, this age group appears to be most affected by influenza B/Victoria.

Strain characterizations

From September 1, 2023, to August 15, 2024, the National Microbiology Laboratory Branch has characterized 1,999 influenza viruses (334 A(H3N2), 920 A(H1N1) and 745 influenza B) received from Canadian laboratories.

Figure 3: Proportion of influenza B detections by age group according to seasonal influenza B lineage dominance, Canada, seasons 2015–2016 to 2019–2020 and 2022–2023 to 2023–2024[a]



[a] The 2020–2021 and 2021–2022 seasons are excluded from this figure due to lack of substantial influenza circulation and the 2019–2020 season was truncated due to the COVID-19 pandemic

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 2023–2024 Northern Hemisphere influenza vaccine are B/Austria/1359417/2021 (Victoria lineage) and B/Phuket/3073/2013 (Yamagata lineage). All 745 influenza B viruses characterized were antigenically similar to B/Austria/1359417/2021. Additionally, 556 influenza B viruses underwent testing for antiviral resistance and all were sensitive to oseltamivir and zanamivir.

Age of detections by influenza B strain were provided by the National Microbiology Laboratory dating from the 2014–2015 season up to July 2024. Over a total of 6,070 detections for which age and influenza B strain information were provided, a clear trend emerged with respect to the age distribution of influenza B/Victoria detections and influenza B/Yamagata detections (**Table 1**). Influenza B/Victoria detections are concentrated among younger age groups, with nearly 60% of detections occurring in children aged 0–19 years; however, the trend is reversed in influenza B/Yamagata detections, with more than 50% of detections occurring in the two oldest age groups (45–64 years and 65 years and older).

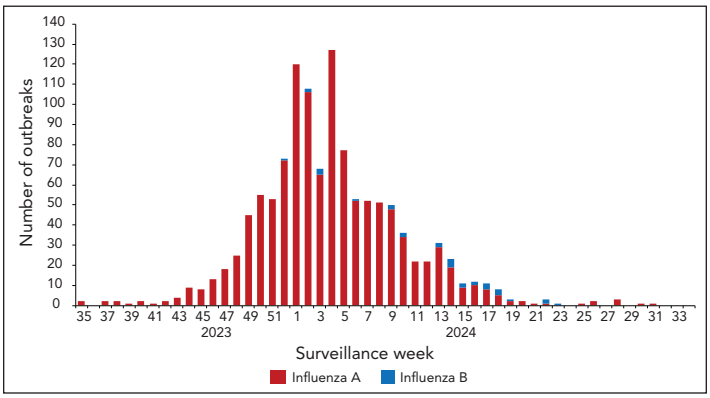
Table 1: Influenza B viruses characterized by the National Microbiology Laboratory Branch by age group, seasons 2014–2015 to 2023–2024

Age group (years)	Influenza B viruses characterized by the National Microbiology Laboratory Branch (seasons 2014–2015 to 2023–2024)		
	Victoria (N=2,577)	Yamagata (N=3,493)	Total (N=6,070)
0–4	503 (19.5%)	258 (7.4%)	761 (12.5%)
5–19	994 (38.6%)	669 (19.2%)	1,663 (27.4%)
20–44	715 (27.7%)	566 (16.2%)	1,281 (21.1%)
45–64	208 (8.1%)	906 (25.9%)	1,114 (18.4%)
65 and older	157 (6.1%)	1,094 (31.3%)	1,251 (20.6%)

Outbreaks

In the 2023–2024 season, a total of 1,224 influenza-associated outbreaks were reported. The majority (53%) were declared in long-term care facilities, followed by 27% in acute care facilities. Despite the wave of influenza B activity late in the season (starting in week 52, week ending December 20, 2023), outbreaks reported during this wave remained primarily associated with influenza A (**Figure 4**). In total, very few outbreaks this season were associated with influenza B, which is typical in pre-pandemic influenza seasons (6) (31 outbreaks or 2.5% of reported laboratory-confirmed outbreaks). Among long-term care facilities, 3% of reported laboratory-confirmed outbreaks were associated with influenza B.

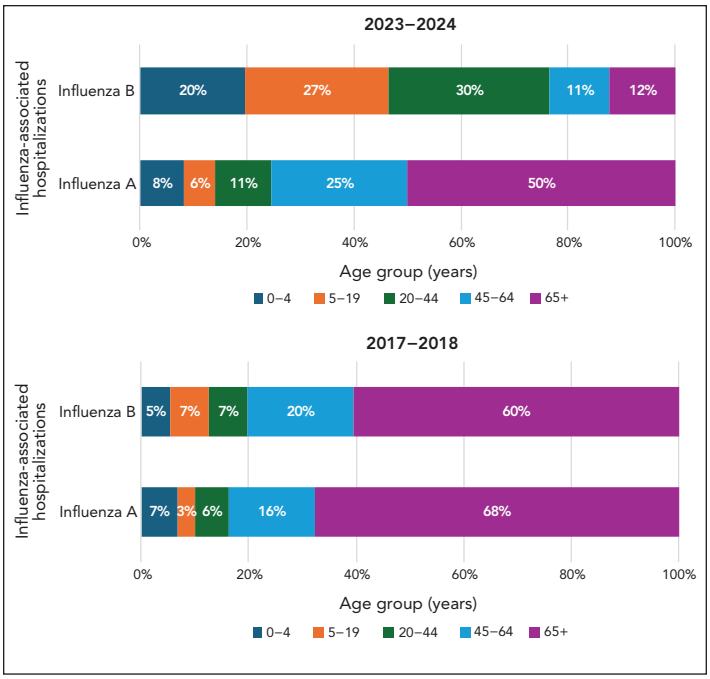
Figure 4: Number of laboratory-confirmed influenza-associated outbreaks by type, Canada, season 2023–2024



Severe outcomes

In the 2023–2024 season, 4,516 influenza-associated hospitalizations were reported by participating provinces and territories (influenza-associated hospitalizations are reported by Alberta, New Brunswick, Newfoundland and Labrador, Prince Edward Island and Yukon). Among these, 597 (13%) were due to influenza B. Among influenza B hospitalizations, 46.4% were among children aged 0–19 years, compared to only 12.2% among adults aged 65 years and older. This is in contrast to influenza A, where among the 3,919 influenza A hospitalizations, 14.1% occurred among children aged 0–19 years, compared to 50% among adults aged 65 years and older (**Figure 5**). These hospitalizations trends contrast the most recent influenza B/Yamagata dominant season in 2017–2018, where the age distribution of influenza-associated hospitalizations was similar between influenza A and influenza B (notably, the majority of hospitalizations, regardless of influenza type occurred in adults aged 65 years and older). These two seasons are the most comparable in terms of influenza B activity, as they are the most similar with respect to the total number of influenza B detections and only differ in dominant B lineage in circulation. In 2017–2018, a total of 23,772 influenza B detections were reported (7), compared to 23,233 detections in the 2023–2024 season.

Figure 5: Influenza-associated hospitalizations by type and age group, Canada, season 2023–2024 compared to season 2017–2018



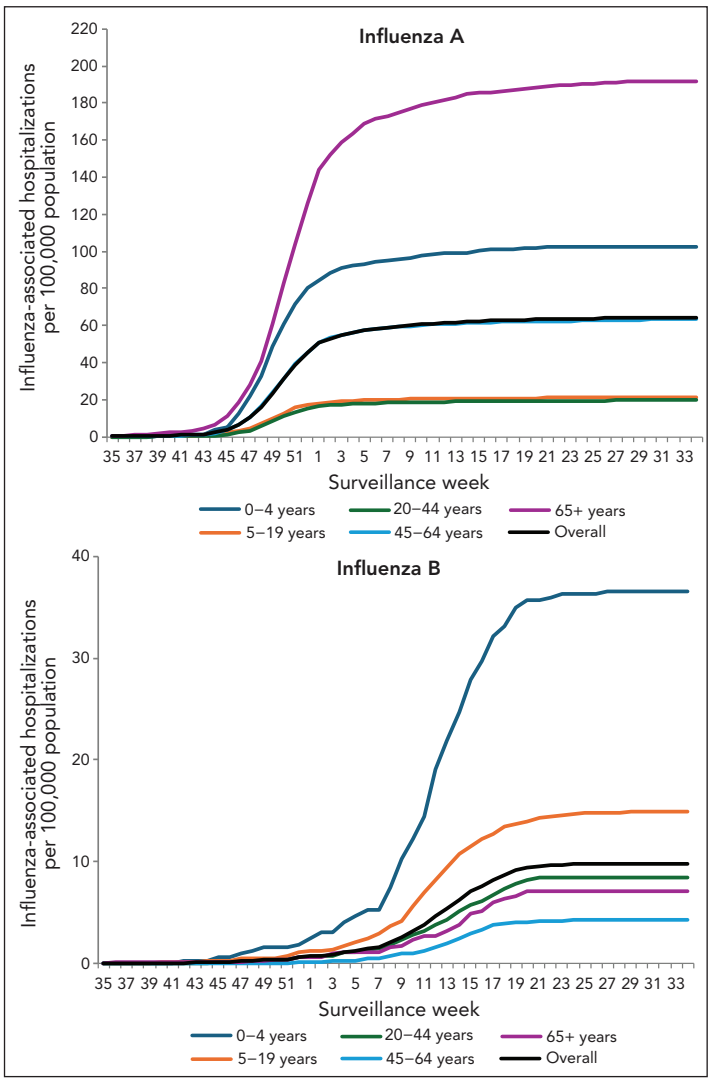
Nearly all influenza B-associated hospitalizations occurred during the influenza B wave late in the season. The cumulative influenza A-associated hospitalization rate for the 2023–2024 season follows a typical pattern, plateauing around the season peak; however, the cumulative influenza B-associated hospitalization rate only plateaus following the season's influenza B peak (**Figure 6**). The highest cumulative hospitalization rates for influenza A were among adults aged 65 years and older (n=192 per 100,000 population) and children younger than five years (n=102 per 100,000 population), whereas the highest cumulative hospitalization rates for influenza B were among children younger than five years (n=37 per 100,000 population) and children between the ages of 5–19 years (n=15 per 100,000 population).

Vaccine effectiveness

With contribution from the provinces of British Columbia, Alberta, Ontario and Québec, the Canadian Sentinel Practitioner Surveillance Network provides vaccine effectiveness estimates for the prevention of medically attended illness due to laboratory-confirmed influenza and COVID-19.

Between October 29, 2023, and May 4, 2024, influenza A(H1N1) pdm09 comprised about half, influenza B about one-quarter and influenza A(H3N2) about one-fifth of all influenza viruses detected by the Sentinel Practitioner Surveillance Network. All influenza B viruses were the vaccine matched B(Victoria) V1A.3a.2 clade. During the analysis period, vaccine effectiveness against any medically attended influenza was 46% (95% confidence interval [CI]: 37%–54%). Vaccine effectiveness against influenza B was 63% (95% CI: 48%–74%) (8).

Figure 6: Cumulative rates of influenza-associated hospitalizations by age-group, type and surveillance week, Canada, participating provinces and territories[a,b]



[a] Note the different scales used in the two figure panels
[b] These figures are likely an underestimate of the true cumulative hospitalization rates due to the small number of reporting provinces and territories over the course of the season

For more information regarding influenza vaccine effectiveness for the 2023–2024 season, including information regarding influenza A vaccine effectiveness, please consult the week 34 FluWatch report (2).

Discussion

The 2023–2024 influenza epidemic, in contrast with the several prior extraordinary seasons, appeared to be remarkably familiar. The return of pre-pandemic expected levels of influenza B activity stands out as a key feature of this season, while the persisting absence of influenza B/Yamagata raises questions about the evolving burden of influenza B. The apparent disappearance of influenza B/Yamagata has previously been discussed as a phenomenon that may incur notable implications on population level impacts of influenza B (1). While the

2022–2023 season did see typical late-season influenza B activity, it was less pronounced compared to the 2023–2024 season. In the 2022–2023 season, influenza B percent positivity reached a peak of 1.9% (9), compared to this season's peak of 6.8%. The return of pre-pandemic-scale influenza B activity has been observed across North America and other regions of the Northern Hemisphere (10); yet according to global sources, no naturally occurring detection of influenza B/Yamagata has been confirmed worldwide since March 2020 (4). Since March 2020, only sporadic detections of influenza B/Yamagata have been reported, primarily from vaccine-derived cases or attributed to data entry errors (11,12).

The global shift towards influenza B/Victoria predominance has several implications for the field of seasonal influenza surveillance. Notably, the marked difference in affected age groups during B/Victoria seasons compared with B/Yamagata seasons implies a shift in burden of influenza B from older to younger age groups (11,13). It is important to note that influenza B typically circulates in much lower volumes than influenza A (1). While influenza A is the main contributor to the global burden of influenza, influenza B trends can push or pull seasonal severity by impacting the demographics upon which the burden falls.

Influenza B/Victoria is associated to a greater rate of infection in children (14). This demographic trend is apparent when comparing the age distribution of influenza B detections from season to season. Analysis of three influenza B/Victoria-dominant seasons (2023–2024, 2018–2019 and 2015–2016) indicates that detections occur primarily in younger age groups (0–19 years), as well as in those aged 20–44 years. The opposite is true of the B/Yamagata-dominant seasons illustrated (2017–2018 and 2016–2017), where older age groups (45 years and older) account for over 50% of seasons influenza B detections. This is further demonstrated through the age-specific strain characterization data for influenza B detections from the National Microbiology Laboratory Branch. Although not all detections are characterized every season, the random sample of influenza B detections that have been characterized, notably in seasons where influenza B/Victoria and influenza B/Yamagata co-circulated, reflect the consistent lineage-based age distribution.

Hospitalization data from this season and seasons past provides valuable insight into the impact of influenza B/Victoria on young children and youths. When comparing the age distribution of influenza-associated hospitalizations by age group between a B/Victoria-dominant season and a B/Yamagata-dominant season it is evident that there is a shift in the distribution of hospitalizations among age groups. While pediatric influenza B-associated hospitalizations account for nearly half of all influenza B associated hospitalizations in the 2023–2024 B/Victoria season, they only account for 12% of all influenza B associated hospitalizations in the 2017–2018 B/Yamagata season. There is a perception that influenza B infections are milder than those of influenza A; however, there are emerging studies that suggest variation in severity among the pediatric population, especially the hospitalized pediatric population (15). This underscores the importance of seasonal influenza vaccination among the pediatric population. Seasonal influenza vaccination remains a crucial component of seasonal influenza prevention practices. This season, influenza vaccination effectiveness against medically attended influenza B was 63% (95% CI: 48%–74%).

This shift in burden may also be perceived as a reduction in the burden of influenza on older demographics. Pre-pandemic, older demographics were consistently exposed to a higher risk of severe outcomes from influenza infection throughout the season. However, a shift in the burden of influenza B towards younger demographics as a result of the predominance of influenza B/Victoria may result in a reduction in overall disease burden relative to pre-pandemic years (11,16). This is evidenced by both the influenza type-specific outbreaks trends and the cumulative hospitalization rates for the 2023–2024 season. Despite the distinct wave of influenza B activity in the second half of the season, influenza B associated outbreaks in long-term care facilities, where the majority of residents are older adults aged 65 years and older, accounted for 3% of reported outbreaks. Among the hospitalization data, the highest cumulative influenza A-associated hospitalization rates were reported in adults aged 65 years and older (n=192 per 100,000 population) followed by those aged 0–4 years (n=102 per 100,000 population). However, the difference in magnitude between these two demographics is more pronounced when analyzing the influenza B associated cumulative hospitalization rate, where children aged 0–4 years face the highest burden (n=37 per 100,000 population)—more than five times higher than that of adults aged 65 years and older (n=7 per 100,000 population). These figures are likely an underestimate of the true cumulative hospitalization rates due to the small number of reporting provinces and territories over the course of the season. Nonetheless, the trends remain apparent, and older demographics have been less affected by influenza B/Victoria-dominant seasons. Continued monitoring for changes to the burden of influenza B/Victoria will be important to understand whether influenza B/Victoria trends are evolving, and how these trends are affecting the overall burden of influenza.

Despite the lack of circulation of naturally occurring influenza B/Yamagata, the extinction of the lineage has not yet been declared, nor has there been any scientific expert discussion on the criteria required to declare its extinction (12). The continued characterization of influenza B specimens is required to monitor for the potential resurgence of B/Yamagata. With the global move of surveillance programs to engage in the surveillance of multiple priority respiratory pathogens (SARS-CoV-2, influenza and respiratory syncytial virus) using one integrated surveillance platform, it is important to consider that a "one-size-fits-all" approach may not be sufficient to monitor the nuances of the influenza virus. The evolving landscape of influenza viruses is

marking the beginning of a precarious phase for respiratory virus surveillance: future seasonal vaccines will no longer include the influenza B/Yamagata strain, new respiratory syncytial virus therapeutics have the potential to alter viral circulation dynamics in certain populations, and SARS-CoV-2 continues to co-circulate at various phases of the season. To effectively inform influenza-specific prevention policies, it is essential to maintain all components, both virological and epidemiological, of comprehensive surveillance programs such as FluWatch.

Authors' statement

MB — Conceptualization, methodology, formal analysis, writing–original draft, visualization
AN — Writing–review & editing
KS — Data curation, conceptualization
SB — Software, data curation
AR — Software, data curation
LL — Conceptualization, methodology, writing–review & editing
AS — Supervision, writing–review & editing
NB — Data curation, investigation

Competing interests

None.

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Perspectives on blastomycosis in Canada in the face of climate change

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Abstract

Blastomycosis is a disease of potentially varied presentations caused by thermally dimorphic fungi that appear as mold at ambient temperatures and transform to yeast at body temperature. Inhalation of aerosolized fungal spores represents the primary mode of transmission. Exposure may follow outdoor activities that disturb soil, which is warm, moist, acidic and rich in organic debris, particularly within forested areas and in proximity to waterways. Blastomycosis is endemic to several parts of Canada, but is only reportable in Ontario and Manitoba, with Northwestern Ontario being considered a hyperendemic area with average annual incidence rates of over 25 cases per 100,000 population. Delays in diagnosis and treatment are frequently observed as the symptoms and imaging findings of blastomycosis may initially be mistaken for community-acquired pneumonia, tuberculosis or malignancy, which can result in interim disease progression and worsening clinical outcomes. Risks from fungal infections such as blastomycosis are likely to increase with climate change-associated shifts in temperature and rainfall, and this may contribute to the geographic expansion of cases, a phenomenon that appears to be already underway. Further research investigating the ecological niche of *Blastomyces* and its climate sensitivity could help facilitate better modelling of the potential impacts of climate change on risks to Canadians and inform more effective methods of exposure prevention. Early clinical recognition and treatment of blastomycosis remain the key to minimizing morbidity and mortality.

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Keywords: blastomycosis, endemic, Canada, climate change, ecological niche, thermally dimorphic fungi, geographic distribution

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Introduction

Background

Blastomycosis is endemic to North America, particularly in areas bordering the Great Lakes, St. Lawrence Seaway and Mississippi and Ohio Rivers, though there is some evidence that the geographic distribution of blastomycosis is expanding beyond these historical margins (1–4). *Blastomyces dermatitidis* and *Blastomyces gilchristii* are the predominant fungal species that cause blastomycosis in North America (5). Sporadic cases attributed to *Blastomyces helicus* have also been reported in western Canada and the United States (US), though these cases are characterized by an atypical geographic range, mycological features and clinical epidemiology (6–8). In contrast to cases associated with *B. dermatitidis* and *B. gilchristii,* which most frequently involve immunocompetent individuals, *B. helicus* is opportunistic, mainly affecting those who are immunocompromised (6–8). Other species that have been described include 1) *B. percursus*, found in Africa and the Middle East; 2) *B. emzantsi*, found in South Africa; 3) *B. parvus*, reported to cause a rare pulmonary illness distinct from blastomycosis, called adiaspiromycosis, in North and South America, Eastern Europe and Australia; and 4) *B. silverae*, which has been identified in western Canada and is not currently known to cause disease in humans (8–10). *Blastomyces dermatitidis* and *B. gilchristii,* the more commonly encountered *Blastomyces* spp. in North America, are examples of thermally dimorphic fungi that grow as mold in the environment at ambient temperatures, but which, once spores and mold fragments are released into the air and inhaled, convert to thick-walled, broad-based budding yeast at body temperature in tissues, resulting in morbidity in approximately half of infected individuals (11,12).

Objectives

As the burden of blastomycosis in Canada is likely under-recognized and under-reported, the objective of this overview was to synthesize the clinical and epidemiological evidence

regarding blastomycosis in Canada to improve awareness about this disease, highlighting the potential impacts of climate change as well as current knowledge gaps and future directions.

Methods

This literature review included a search for articles in PubMed and EBSCOhost databases using keywords related to blastomycosis and narrowed to literature conducted in North America from January 1, 2010, to June 9, 2024. The search was augmented by the evaluation of reference lists from the *Health of Canadians in a Changing Climate* report (13) and several relevant primary research studies and literature reviews (available upon request) to identify work omitted by the database search until we reached saturation. Grey literature was identified by implementing the search strategy in Google and screening the search results, stopping at the point where no new relevant results were identified on a page, and through targeted searches within the websites of key public health agencies in North America. Citations were screened for relevance and inclusion in the review with a focus on evidence from Canada. Where applicable, citations for older evidence were replaced by newer evidence to ensure this review was a good reflection of the most recent evidence on blastomycosis.

Discussion

Incidence and trends in Canada

Within Canada, blastomycosis has been detected in areas of Ontario, Québec, Manitoba, Saskatchewan, Alberta, Nova Scotia and New Brunswick, but is only a reportable disease in Ontario as of mid-2018 and in Manitoba since 2006 (11,14–23). In endemic areas, where the disease is reportable, incidence rates typically are 0.4–1.3 cases per 100,000 population per year (22,24,25); however, hyperendemic areas such as Northwestern Ontario, represented by the catchment area of the Northwestern Health Unit, have reported average incidence rates of over 25 cases per 100,000 population per year (range: 15–43 cases per 100,000 population per year) (21,26–28). In comparison, blastomycosis in the US is reportable in Arkansas, Louisiana, Colorado, Michigan, Minnesota and Wisconsin, where the annual incidence is two or fewer cases per 100,000 population, while hyperendemic areas in several northern counties of Wisconsin report annual rates in the range of 10–40 cases per 100,000 population (29–31). Given that blastomycosis is not a nationally notifiable disease either in Canada or the US, and in light of frequent asymptomatic infections and missed or delayed diagnoses, there is likely significant under-reporting of cases and under-estimation of its true incidence (12,32–36).

Although there has not been consistent surveillance in affected areas of Canada to establish definite trends in the incidence of blastomycosis, several studies suggest that cases have been increasing in some areas over time (14,15,33,37). The observed increases may be due to improving surveillance, increasing healthcare provider and/or community awareness of the infection, or possibly an expanding ecological niche for *Blastomyces* (33,37,38). It has been suggested that cases in dogs, whose incidence is estimated to be eight times greater than that of humans, may serve as sentinels for cases in humans (39–42). The high incidence in dogs could be related to the time spent outdoors, close contact with soil and such behaviours as digging and sniffing, which can increase exposure to fungal spores (40).

Epidemiological investigations suggest most human cases of blastomycosis are sporadic; however, a smaller proportion occur as outbreaks with epidemiologic links to a likely common source (29,36,43,44). Canadians are most commonly exposed during the warmer summer months when both the climate and human activities are more favourable for exposure; this leads to a majority of cases being diagnosed in the fall and winter, following an appropriate incubation period (11,14,33,45–48). In the US, no seasonal pattern was observed for blastomycosis-related hospital admissions during the period 2010–2020 (49).

Ecological factors

The ecology of *Blastomyces* is not well understood due to challenges in conducting epidemiological investigations that aim to identify a potential source, given the long latency period of up to 15 weeks from exposure to clinical onset (31). Further challenges exist in recovering the fungus from the environment as *Blastomyces* is found to compete poorly with other microflora present in natural soil (38,50–52). Studies have reported the failure to repeat the isolation of *Blastomyces* at later time points from previously positive sample sites, suggesting that its growth can be sporadic and perhaps contingent on short-lived climactic and environmental conditions (52,53). Large outbreaks over an extended duration have been reported where optimal growth conditions are presumably stable, such as an outbreak spanning 10 weeks in Wisconsin in 2015 associated with recreational tubing along a river (54).

To date, research characterizing the environmental niche of *Blastomyces* suggests that moist soil with high organic content (e.g., rotting wood, decaying vegetation, animal manure) and acidic pH near lakes and rivers or in wooded areas is well suited for *Blastomyces* spp. survival (52,53,55–58). Laboratory and outbreak investigations also indicate that recent rainfall is important for the recovery of *Blastomyces* from environmental samples and the release of spores into the environment, which are then dispersed during windy weather (52,56,59–62). While outbreaks have occurred in the relative absence of rain too, other factors may have been present that created favourable conditions for transmission, such as proximity to waterways and/or soil-disrupting activity (54,63).

Risk groups

Risk of exposure can increase with human activities that disturb soil and aerosolize spores, including occupations involving high-risk outdoor activities such as construction, excavation, landscaping and forestry work (1,34,38,48,57,60,64–67). Other exposures may come from outdoor recreational activities, including hunting, fishing, canoeing, camping, hiking and the use of all-terrain vehicles (ATVs), which involve close contact with soil and decaying vegetation near waterways (1,38,46,55,64,68,69).

The majority of clinical cases occur in adults (mostly middle-aged adults 30–59 years of age) with less than 13% occurring in children (11,12,14,16,26,45,62,70). Males are more frequently affected than females, which may reflect a greater likelihood of occupational or recreational environmental exposures (38); however, a sex-specific, possibly hormonally mediated, susceptibility to infection has been proposed as a factor in another endemic dimorphic mycosis that predominates in males, namely coccidioidomycosis (71,72).

Indigenous Peoples in Ontario and Manitoba have been found to be disproportionately affected by blastomycosis (11,33,46). Similarly, in the US, incidence rates among Native American and Alaska Native Peoples between 2010 and 2020 were approximately six times higher than in non-Hispanic Whites (71). A genetic predisposition may account for these findings, but alternate explanations include differences in occupational or recreational exposures, access to medical care, socioeconomic status and/or other social determinants of health (12,36,38,71). Higher rates of comorbidities and smoking among Indigenous Peoples in Northwestern Ontario were also offered as possible contributing factors (33).

Clinical features of blastomycosis

The primary route of *Blastomyces* transmission is through the inhalation of aerosolized spores; however, infection has also been documented from direct cutaneous inoculation by traumatic injury (e.g., needlestick injuries in laboratory workers or veterinarians) or following a bite or scratch from an infected animal (73–76). Isolated case reports of possible sexual transmission appear in the literature, along with rare reports of perinatal transmission (77–81).

The incubation period of blastomycosis is estimated to be 30 to 45 days for inhalational exposure with a possible range of 14 to 106 days, whereas the incubation period for primary cutaneous inoculation is approximately two weeks (26,54,55,73,78).

The clinical spectrum of disease includes subclinical infection in approximately 50% of cases; acute pneumonia, indistinguishable from community-acquired bacterial pneumonia; chronic pneumonia, mimicking tuberculosis (cavitary lesions, miliary pattern) or malignancy (nodules, masses); and, at the most severe end of the spectrum, lung infection may progress to acute respiratory distress syndrome (ARDS) in 8%–15% of cases (7,8,55,82–84). Symptoms of acute pulmonary blastomycosis consist of fever, chills, headache, productive or non-productive cough, shortness of breath, chest pain and malaise (12). Symptoms of chronic pulmonary blastomycosis include fever, chills, persistent cough, hemoptysis, night sweats, decreased appetite and weight loss, which can be readily mistaken for the clinical signs of tuberculosis or cancer (12). Hematogenous dissemination occurs in 25%–40% of cases (12). Upon dissemination, any organ can potentially become involved, though the most commonly affected organ systems are the skin, followed by the bones and joints (e.g., long bones, thoracolumbar spine, ribs, skull), genitourinary tract (e.g., prostatitis, epididymo-orchitis) and central nervous system (CNS), where blastomycosis can present as meningitis, epidural abscesses, intracranial abscesses or other space-occupying lesions (i.e., granulomas) (34,43,85–88). Cutaneous disease may appear as single or multiple verrucous, nodular or ulcerative lesions on the face and distal extremities that are often marked by sharp, irregular borders, crusting and the formation of micro-abscesses in the underlying subcutaneous tissue (43,89).

The variety of clinical presentations of blastomycosis and their similarities to other conditions present challenges to early diagnosis. In a retrospective chart review, a median of 2.5 courses of antibiotics (interquartile range [IQR]: 1.5–4.5 courses) were prescribed prior to a diagnosis of pulmonary blastomycosis and a median of 23 days (IQR: 8–36 days) passed from the initial presentation to a healthcare facility before the correct diagnosis was made (35). Like pulmonary blastomycosis, cutaneous blastomycosis is often misdiagnosed as other pathologies such as basal cell or squamous cell carcinoma, keratoacanthoma, pyoderma gangrenosum (associated with autoimmune disease) or cutaneous tuberculosis (7,76,90,91). Osteomyelitis resulting from *Blastomyces* infection can mimic cancer (appearing as masses or lytic lesions on imaging) or skeletal tuberculosis (7). Further underpinning its reputation as a great masquerader, meningitis due to disseminated blastomycosis is frequently misdiagnosed as tuberculous meningitis, while blastomycosis-associated spinal or intracranial space-occupying lesions can be mistaken for malignancy (7,86–88,92).

A few studies have reported on the differences in clinical presentation and/or clinical severity between cases infected with *B. dermatitidis* compared to *B. gilchristii*. One study conducted in Québec, Canada found no association between *Blastomyces* genotype and the proportion of severe or fatal cases; however, only 2% of the patients in their sample were infected with *B. gilchristii*, reducing its power to discriminate clinically between species (93). A more recent study conducted in Wisconsin found that patients infected with *B. gilchristii* (n=80) were more likely to be hospitalized than those with *B. dermatitidis* (n=40), though the difference was no longer statistically significant following multivariate regression analysis (p=0.06) (94). Additional variation in clinical presentations between species was noted, where patients infected with *B. gilchristii* were more likely to

present with fever ($p<0.05$) and those with *B. dermatitidis* had a significantly higher rate of developing disseminated infection with skin lesions ($p<0.05$) (94).

The mortality rate for blastomycosis was estimated in a 2020 systematic review and meta-analysis, which found an overall pooled mortality of 6.6% (95% CI: 4.9%–8.2%) across diagnosed cases of blastomycosis (32). This estimate is in relative agreement with studies from the US that estimated mortality to be 6.9%–10% (36,49,68,71,95); however, the US Centers for Disease Control and Prevention recently reported that the case fatality rate for blastomycosis across the five states where the disease was reportable rose to 17% in 2021, almost double the rate in 2019 (96). This sharp jump may be related to overwhelmed healthcare systems during the pandemic and patient hesitancy to seek medical care, which may have exacerbated diagnostic and treatment delays, leading to more severe disease presentations (96).

Risk factors associated with mortality and/or severe disease have included older age, immunosuppression, multi-lobar pulmonary involvement, ARDS and chronic disease (e.g., malignancy, chronic obstructive pulmonary disease, chronic lung disease, obesity, diabetes) (32,49,68,93,97). While the current evidence suggests that being immunocompromised is not a risk factor for developing blastomycosis, infection is more severe among those who are immunocompromised (34). The previously cited meta-analysis found that the pooled mortality rate was more than five times higher among patients who were immunocompromised (37%; 95% CI: 23%–51%) compared to general patients (6.6%; 95% CI: 4.9%–8.2%) (32). When complicated by ARDS, the mortality rate of blastomycosis reached 75% (95% CI: 53%–96%) (32).

Laboratory diagnosis

The gold standard for the diagnosis of blastomycosis is by culture of sputum, tracheal aspirates, bronchoalveolar lavage fluid, cerebrospinal fluid, urine or biopsied tissue, but results can take 1–4 weeks (34). Microscopic visualization of yeast cells in smears or tissue specimens following the application of 10% potassium hydroxide and/or a fungal stain can offer a more rapid diagnosis, but this method is less sensitive than culture, so a negative result does not exclude a diagnosis of blastomycosis (38).

Serological tests have been available for decades, but their diagnostic value is limited by poor sensitivity, particularly early in infection and among patients who are immunocompromised (38,81,98). The most sensitive antibody test consisted of an enzyme immunoassay (EIA) that detected antibodies against *Blastomyces* adhesin-1 (BAD-1), a cell wall adhesion antigen and virulence factor. Despite a reported sensitivity of 88% and specificity of 94%–99%, this test has not gained widespread clinical use (7,99).

Enzyme immunoassays detecting a cell wall antigen known as galactomannan in patient body fluids have become a useful diagnostic tool that enables the rapid diagnosis of blastomycosis from a range of samples, including urine, serum, bronchoalveolar lavage fluid or cerebrospinal fluid (8,12). In the US, antigen EIA is a recommended component of diagnostic testing for suspected blastomycosis (98,100); however, in Canada, the adoption of antigen EIAs is reported to be limited (81). The sensitivity of antigen detection by EIA in urine samples of patients with proven disease is 76.3%–92.9% and the specificity is 79.3%, while the sensitivity of antigen EIA using serum as the sample source is somewhat lower, ranging from 56%–82% (98,100–103). False-positives can occur due to cross-reactivity with other fungal pathogens, particularly *Histoplasma*, which can be an issue in areas where their respective geographic distributions overlap; fortunately, the recommended treatments for histoplasmosis and blastomycosis are similar, reducing the harm of misdiagnosis (5,100,101,104,105). Note that serologic testing may be helpful for differentiating blastomycosis from histoplasmosis and on occasions when antigen EIAs are negative but suspicion for blastomycosis remains (98). It has been suggested that antigen EIA levels may correlate with disease severity and could be used to monitor the response to blastomycosis treatment, but at least with respect to antigen testing for histoplasmosis, low levels of antigenuria may persist in some patients for months even after successful eradication (8,34,104,106,107).

Advances in the molecular diagnosis of *Blastomyces* infection could help facilitate the workup of patients with possible blastomycosis and reduce diagnostic delays; however PCR-based tests are currently limited to reference laboratories and have not been widely standardized (7,34,106).

Given the imperfect sensitivity and specificity of currently available tests, no single test is sufficiently accurate for diagnosis in isolation (100). In combination with clinical and epidemiological history, physicians often need to use multiple diagnostic methods to get an acceptable level of diagnostic accuracy (98,100).

Treatment

All patients diagnosed with blastomycosis should receive antifungal therapy regardless of the clinical presentation because of the risk of progression or recurrence of symptoms if left untreated (34). Mild to moderate blastomycosis is treated with oral itraconazole, while moderate to severe blastomycosis is initially treated with lipid formulations of amphotericin B for 1–2 weeks until clinical improvement is noted (4–6 weeks in the case of CNS disease), following which, therapy is completed using oral itraconazole (34,104). Total treatment duration is typically 6–12 months and depends on the severity of the infection, immune status of the host and involvement of the bone, joints or CNS (7,34,104). Lifelong suppressive therapy

with oral itraconazole may be required for immunosuppressed patients if immunosuppression cannot be reversed (104).

Several other azoles have been used to treat blastomycosis; however, clinical trial data for these other agents is still limited. For example, a novel formulation of itraconazole is available, called super-bioavailability itraconazole (SUBA-itra), which exhibits enhanced intestinal absorption relative to the conventional formulation with reduced inter-patient pharmacokinetic variability and a lower impact from food and alterations in gastric acidity (108). Voriconazole, a relatively newer azole, has been shown to be effective as an alternative to itraconazole when there is CNS involvement due to its better penetration of the blood brain barrier and excellent *in vitro* activity against *B. dermatitidis*, followed by fluconazole, which also demonstrates good penetration into the CNS and is moderately effective against blastomycosis (8,92,104). Another relatively newer azole, posaconazole, has been used to treat non-CNS blastomycosis, as it penetrates the blood brain barrier poorly but may have more potent fungicidal activity against *Blastomyces* than itraconazole as well as improved oral absorption and fewer adverse effects (8,109). Limited data for oral isavuconazole also exist (7,8,110). Given their narrow therapeutic windows, therapeutic drug monitoring is recommended when using either itraconazole, voriconazole or posaconazole in order to ensure adequate steady-state serum levels and avoid drug-related toxicities (111).

Pregnant patients who are diagnosed with blastomycosis should receive intravenous liposomal amphotericin B without a subsequent azole, due to the teratogenic effects of azoles, until after delivery or until resolution of the infection, whichever occurs first (7). Post-delivery, the placenta should be examined for signs of *Blastomyces* infection, the newborn monitored closely and amphotericin B deoxycholate given if the newborn is found to be infected (7).

Impacts of climate change

The future climate projected for Canada includes increasing temperatures, increasing rainfall (although with more regional variation than for temperature) and a greater fraction of precipitation during the winter occurring as rain rather than snow (13,112). The climate is also expected to become more variable, with an increase in extreme weather events, including heat waves, summertime droughts and more frequent and severe storms that are expected to increase the possibility of flooding (13,112). Risks from fungal infections such as blastomycosis are likely to change with these expected changes in temperature and rainfall (4,13). Globally, over half of known infectious diseases (n=218/375) were found to be potentially exacerbated by the effects of climate change, including blastomycosis and twenty-three other fungal diseases (113). Climate change may also drive changes to the geographic ranges of several dimorphic fungi that are endemic to North America, such as *Coccidioides* in Southwestern US and *Histoplasma* and *Blastomyces* in the US and Canada (3,4,114–116). These changes may be long-lasting or, perhaps, transient and variable. A study conducted in Minnesota reported the transient detection of *Blastomyces* DNA in environmental samples obtained from a non-endemic location following a flood, pointing, once again, to the sometimes evanescent nature of this fungal pathogen when short-term climactic conditions transiently favour fungal growth in otherwise non-conducive environments (117). Climate change may also impact the frequency of cases, and an association between flooding and frequency of blastomycosis cases has been described in the literature (117–120).

Greer *et al.* speculated that the dry summers and heavy wintertime precipitation projected for North America would provide optimal conditions for the dispersal of *Blastomyces* spores (121). Panackal further pointed out that a common pattern emerges among fungal species, in which growth is facilitated by soil moisture from precipitation and humidity, followed by a dry period when fungal hyphae desiccate and form spores, culminating with windy conditions, potentially in the form of storms, hurricanes and tornados, which then aerosolize and disperse the spores over great distances (122). Among several blastomycosis case clusters reported in the literature, exposure was considered to have occurred following periods of diminished precipitation or drought and in association with rainfall events, reinforcing the significance of dry and wet cycles (38,55–57,61–63,123). During abnormally dry days, whose frequency, intensity and duration will increase as the climate continues to grow warmer, winds can disperse fungal spores in the same way that they spread pollen (13).

Conclusion

This review summarizes the evidence regarding blastomycosis in Canada and highlights what is currently known and where important knowledge gaps exist for this fungal disease. While projected to have a larger public health impact due to climate change-associated shifts in temperature and rainfall, our understanding of the interplay between blastomycosis and environmental factors is far from complete (2–4,13,121–128). Further study of *Blastomyces'* ecological niche and climate sensitivity will require novel approaches and greater laboratory test capacity to isolate the pathogen from the environment (129). This could, in turn, facilitate improved modelling of the potential impacts of climate change on risks to the public and help inform more effective measures for prevention (38).

Bearing in mind the uncertainties concerning the current and future epidemiology of blastomycosis, the most important factor in limiting morbidity and mortality is increasing healthcare providers' awareness of blastomycosis to ensure timely diagnosis and treatment and prevent more serious progression of disease. In the event of outbreaks, early clinical recognition also leads to the early engagement of public health authorities, who can

introduce measures to limit ongoing exposures and prevent new cases. Finally, increased awareness among the public living in endemic/hyperendemic areas, particularly those at higher risk, such as Indigenous Peoples and individuals who are immunocompromised, can empower them to ask their healthcare providers about the possibility of blastomycosis should they develop compatible symptoms.

In addition to promoting greater education and awareness, other key measures to consider include the following: funding research to close knowledge gaps regarding the ecology of *Blastomyces*; improving surveillance by making blastomycosis more widely reportable; developing rapid, accurate and standardized PCR-based assays to improve timely case detection; exploring the potential of computer-aided diagnosis using artificial intelligence and machine learning models that could prompt physicians to consider blastomycosis early in the diagnostic process (111,130,131); and finally, developing safer and better-tolerated antifungal treatments to maximize treatment adherence, especially in view of the prolonged length of therapy that can be required for this disease.

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AK — Principal writer, writing–original draft, writing–review & editing
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Locally acquired typhoid fever outbreak linked to chronic carriage in Ottawa, Canada, 2018–2022

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Abstract

Background: In Canada, *Salmonella enterica* serovar Typhi infections are uncommon and typically travel-related. In November 2021, Ottawa Public Health identified a link between two typhoid fever cases, with no recent history of international travel, to the same grocery store ready-to-eat counter.

Objective: This report describes the outbreak response to a rare occurrence of chronic *S.* Typhi carriage in Ottawa, Ontario, Canada and provides recommendations for investigations of small-scale protracted outbreaks.

Methods: We administered exposure questionnaires using a single interviewer approach, tested stool samples of contacts and food handlers, inspected food premises, collected food samples and reviewed takeout receipts. Social network, spatial and whole genome sequencing analyses were used to investigate additional possible links between cases.

Results: Seven people with typhoid fever and onset from October 2018 to May 2022 were linked to an asymptomatic chronic *S.* Typhi carrier. Whole-genome sequencing confirmed that all eight isolates matched the outbreak cluster. All cases and carrier resided within an eight km radius in Ottawa. The chronic carrier worked as a food handler at various locations of a grocery store chain, including the implicated ready-to-eat counter. Transmission occurred via food handling, shared workspaces and social and household networks.

Conclusion: The chronic carrier was excluded from food handling until successful completion of treatment and clearance testing. We overcame the challenges of a small but prolonged outbreak by identifying an asymptomatic carrier using a multi-method approach including whole genome sequencing and social network analysis.

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Introduction

Typhoid fever is caused by direct or indirect fecal-oral exposure from an individual infected with *Salmonella enterica* serovar Typhi (*S.* Typhi). The primary incubation period is typically eight to 14 days but can range from three to more than 60 days. Symptoms can be non-specific, ranging from fever and mild illness to severe and potentially fatal illness requiring hospitalization (1). While most infections resolve with treatment, approximately 2%–5% of those infected become chronic carriers who can continue to transmit the bacteria for many years, often without symptoms (2).

Typhoid fever is a notifiable disease in Canada, and in Ontario, cases are reportable to the local Medical Officer of Health (3,4). Due to historic improvements to drinking water, sanitation and food safety, typhoid fever is uncommon in Canada (1,5,6). Between 2012 and 2021, an average of 140 cases per year

were reported (average rate 0.4 per 100,000 population) (6). Most infections are associated with recent international travel, particularly visiting of friends and relatives in endemic regions (7–11). The most recent published report of a locally acquired typhoid fever outbreak in Canada was in Ontario in 1990, linked to consuming raw contaminated imported shellfish (12).

Between 2016 and 2020, an average of four cases of typhoid fever were reported per year in Ottawa, Ontario. In November 2021, Ottawa Public Health identified two locally acquired typhoid fever cases (cases D and E), residing 2.6 km apart, who had been reported two months apart, in September and November 2021, respectively. Case interviews identified linkage to a grocery store ready-to-eat food counter, one as a customer (case D) and the other as an employee (case E). An outbreak was declared in November 2021 and a multi-disciplinary team was assembled to identify the source of the outbreak and implement control measures. Preliminary whole-genome sequencing (WGS) confirmed these cases were related.

This report describes the outbreak response to a rare occurrence of chronic *S.* Typhi carriage in Canada and highlights the strengths of using a multi-method approach to overcome the challenges of investigating small-scale protracted outbreaks.

Methods

Case definition

A confirmed outbreak case was defined as a resident or visitor to Ottawa with laboratory confirmed *S.* Typhi infection and an isolate matching the outbreak cluster within 10 alleles by whole-genome multi-locus sequence typing (wgMLST). Probable cases included persons with laboratory confirmed *S.* Typhi infection awaiting WGS and an epidemiological link to a confirmed case. Suspect cases included persons with laboratory confirmed *Salmonella* infection awaiting serotyping and WGS, who had clinically compatible signs and symptoms of typhoid fever and an epidemiological link to a confirmed case. The case definitions do not specify a time frame as the potential period of exposure was unclear.

Close contacts were defined as household members, colleagues working in proximity and sexual partners of confirmed cases. Testing for *S.* Typhi was offered to all close contacts, with or without symptoms, using two stool samples collected at least 48 hours apart.

Epidemiological investigation

Ottawa Public Health reviewed all typhoid fever cases reported in Ottawa since 2017 to identify any other potentially non-travel related cases. As much as possible, cases were interviewed by a single interviewer and some interviews were conducted in person. Cases were first interviewed using the Ontario standardized Salmonellosis Investigation Tool which gathers exposure information, including a detailed food history, for the seven days prior to symptom onset. Once *S.* Typhi infection was suspected or confirmed, cases were re-interviewed using the Ontario Typhoid Fever Investigation Tool which focuses on exposures in the three to 60 days before symptom onset (13). The interview included questions about occupation, personal and close contacts' travel and consumption of high-risk foods. Additional questions were added on social contacts, country of origin, date of arrival in Canada and specific exposures based on evolving hypotheses. Cases reported prior to November 2021 were re-interviewed with these additional questions.

Social network and spatial analyses were used to generate hypotheses regarding missing epidemiological links. Addresses of cases and common exposure locations were mapped using the geoOttawa application and statistically significant geographic clustering was confirmed using SaTScan version 10.0. Social networks comprised cases and contacts as nodes with links being sharing meals from common sources, preparing food eaten by cases or contacts and working or socializing together, indicating shared bathroom use. As many clients forget contacts (14), we supplemented interviews by reviewing takeout receipts from digital food delivery apps and public social media accounts to further identify common exposures. Social network diagrams were created using Pajek version 5.14.

Laboratory investigation

In Ontario, all *S.* Typhi isolates undergo WGS at Public Health Ontario through the PulseNet Canada program (15). The programmatic criterion to initially identify an *S.* Typhi genomic cluster is two or more isolates (including at least one clinical isolate), identified within 60 days, with 10 or less allele differences by wgMLST. Given the lack of international travel reported by the two index cases, a broader investigation of all *S.* Typhi isolates in Canada identified by PulseNet Canada since 2017 (when WGS was implemented for all *Salmonella* isolates) with 25 or less allele differences by wgMLST was performed to identify any potentially related cases (15). In Ontario, antimicrobial susceptibility testing is routinely performed on *S.* Typhi isolates.

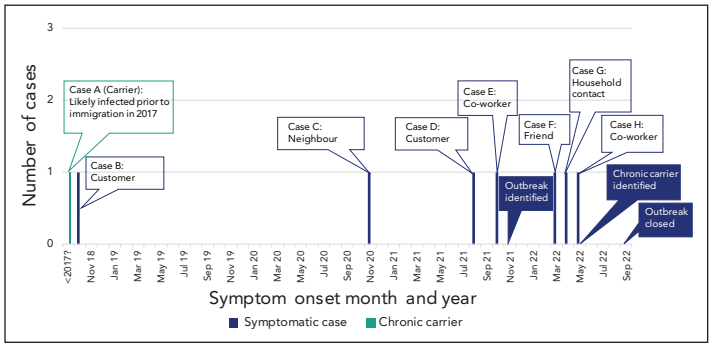
Environmental investigation

Public health inspectors from Ottawa Public Health inspected the grocery store ready-to-eat counter and collected food samples. They observed food handling practices, provided education on hand hygiene, compiled names of food handlers and inquired about illness and travel history. An anonymous survey was also distributed to food handlers to gather information on gastrointestinal and biliary tract illness history. Food handlers were tested for *S.* Typhi using three stool samples each collected at least 48 hours apart, regardless of symptoms.

Results

Seven confirmed cases of typhoid fever with illness onset between October 2018 and May 2022 were linked to an asymptomatic carrier (**Figure 1**). All seven symptomatic cases were interviewed twice. The chronic carrier was interviewed first as a contact and then as a case. Twenty-eight close contacts were also interviewed but no additional cases were identified. Among the seven symptomatic cases, common symptoms included fever (n=7 cases), malaise (n=6), diarrhea (n=5), abdominal pain (n=5) and headache (n=4). Six cases were hospitalized for a median of nine days (range: 5–22 days) and one case received treatment in the emergency department; all recovered. All seven symptomatic cases and carrier resided within an eight km radius in Ottawa. Cases and carrier had a median age of 28 years old (range: 8–50 years) and six (75%) were male. Five of eight (63%) were immigrants to Canada (year of arrival ranged from 1997 to 2019), including four from the same country of origin, but no cases reported recent international travel.

Figure 1: Epidemiological curve of *Salmonella enterica* serovar Typhi confirmed outbreak cases by symptom onset month, Ottawa, 2018–2022



Following the identification of the two index typhoid fever cases (cases D and E) in November 2021, laboratory investigations identified two additional cases (cases B and C) clustering by WGS with illness onset of October 2018 and November 2020, respectively (Figure 1). Of these four initial cases, three (cases B, D, and E) had an epidemiological link to the same grocery store ready-to-eat-counter as either customers (cases B and D) or an employee (case E). At that time, an exposure could not be established for case C. Given the long intervals between case illnesses and epidemiological linkage with the ready-to-eat counter, it was hypothesized that a likely source of transmission was a food handler with chronic *S.* Typhi carriage. Therefore, the initial outbreak investigation focused on the ready-to-eat counter.

Food premises inspections did not identify a source of transmission and no critical infractions were observed. Three food handlers were identified as working at the ready-to-eat counter during the incubation period for cases D and E but were not employed when case B was ill. All three food handlers submitted stool samples which were negative and none reported recent gastrointestinal or biliary tract illness. *Salmonella enterica* serovar Typhi was not detected in any food samples taken from the ready-to-eat counter.

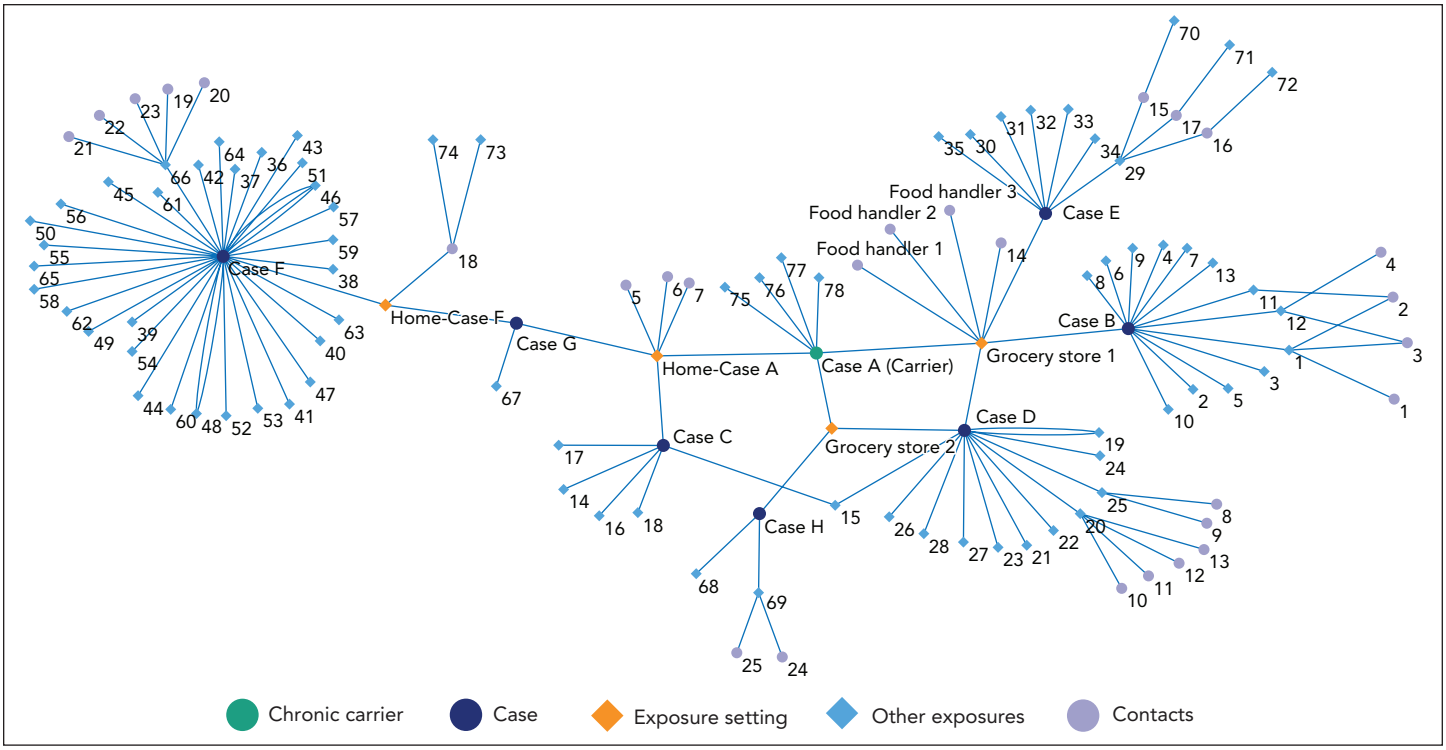
A fifth case (case F) was reported in March 2022. This person had no known epidemiological linkage to the grocery store. They had a common country of origin with case E, suggesting a possible alternative social linkage. The person was interviewed to elicit possible social contacts working as a food handler or connected to previously reported cases; however, they were reluctant to provide information on their contacts.

The sixth (case G) and seventh (case H) cases were reported in May 2022. Contact tracing identified case G as a close contact of case F as well as sharing a common country of origin with cases E and F. Although case G may have been infected via close contact with case F, a common social network between cases F, G and an unidentified chronic *S.* Typhi carrier was also hypothesized. Case H was employed at another location of the same grocery store chain as a janitor. They were not a food handler and did not consume food from the ready-to-eat counter.

Further interviewing identified a short-term household contact of case G who worked as a food handler for the implicated grocery store chain since 2017 at various locations, primarily working at the ready-to-eat counter. This food handler (case A) also shared a common country of origin with cases E, F and G. We hypothesized that this newly identified food handler had chronic *S.* Typhi carriage acquired prior to immigration to Canada in 2017 from their country of origin (Western Pacific region). They were contacted to gather information and request stool testing. Stool cultures came back positive for *S.* Typhi. They were asymptomatic and reported no prior history of gastrointestinal or biliary tract illness.

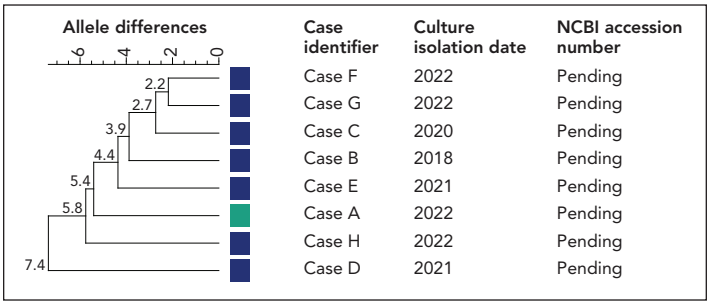
Epidemiological evidence strongly suggested that case A (carrier) was the source case for the outbreak as there were epidemiological links to all cases. Cases B, D, E and H were linked via two grocery store chain locations. Social network and spatial analyses established an epidemiological link with case C as neighbours in the same multi-unit complex (however, with no known direct contact) and with cases F and G as social or household contacts (**Figure 2**). Further, laboratory evidence revealed that all eight outbreak-related *S.* Typhi isolates were closely related within seven alleles by wgMLST (**Figure 3**), and there were no additional *S.* Typhi isolates matching this cluster in Canada since 2017 within the range of 0–25 alleles.

Figure 2: Social network diagram[a] showing linkages between *Salmonella enterica* serovar Typhi outbreak cases and the chronic carrier, Ottawa, 2018–2022



[a] Social network diagram generated using Pajek version 5.14

Figure 3: Phylogenetic tree of *Salmonella enterica* serovar Typhi outbreak-associated isolates, Ottawa, 2018–2022[a]



Case identifier	Culture isolation date	NCBI accession number
Case F	2022	Pending
Case G	2022	Pending
Case C	2020	Pending
Case B	2018	Pending
Case E	2021	Pending
Case A	2022	Pending
Case H	2022	Pending
Case D	2021	Pending

Abbreviation: NCBI, National Centre for Biotechnology Information

[a] Whole-genome multi-locus sequence typing (wgMLST) dendogram generated using BioNumerics version 7. Based on 4,148 *Salmonella* Typhi alleles. The wgMLST allele differences indicated at the nodes were calculated using unweighted pair group method with arithmetic mean (UPGMA)

Public health response

Individuals who met the confirmed, probable or suspect case definitions were excluded from working as food handlers, childcare workers or healthcare providers, until completion of antibiotic treatment and submission of three negative stool samples each collected at least 48 hours apart. Cases and close contacts were counselled on transmission, personal and hand hygiene, food handling, risk of *S.* Typhi carriage and safe sexual practices.

In May 2022, once local transmission was confirmed, an alert to healthcare providers in the region was issued about typhoid fever risk in patients without a travel history.

Case A (carrier) was excluded from food handling work in May 2022. They were referred to an infectious disease specialist and underwent successful susceptibility-informed antibiotic treatment. After treatment, they were cleared to return to work following there consecutive negative stool samples collected at least 48 hours apart (16). In total, case A (carrier) was excluded from food handling work for 59 days and had to find alternate employment due to financial hardship. The outbreak was declared over in September 2022, 120 days (two potential incubation periods) after the onset date of the last outbreak associated case. As of July 2024, no new cases have been identified matching the outbreak cluster.

Discussion

This is the first reported outbreak of locally transmitted typhoid fever in Canada since 1990. Seven cases of typhoid fever over four years (from 2018 to 2022) were linked to an asymptomatic chronic *S.* Typhi carrier who worked irregularly as a food handler at various locations of a grocery store chain. Transmission occurred through food handling, shared workspaces and social and household networks. Although the outbreak was relatively

small, six of seven cases were hospitalized with significant morbidity. This investigation highlights some of the challenges of identifying and managing a typhoid fever outbreak as well as the strengths of using multiple epidemiological, laboratory and environmental investigation methods during outbreak responses.

Characteristics of this outbreak are similar to others reported from non-endemic, high-income countries (5). Locally acquired typhoid fever outbreaks reported in the United States since the 1960s had limited secondary transmission and were often associated with a primary case of chronic *S.* Typhi carriage involved in food handling (5,17–19). This outbreak shares some of the challenges noted in these previous investigations. First, outbreaks caused by chronic *S.* Typhi carriage may be difficult to detect as carriers can shed bacteria intermittently for many years, potentially causing infections over a long period of time (17). Second, a small number of cases and long incubation period can make it more challenging to generate source hypotheses. Finally, given that typhoid fever cases have become infrequent in non-endemic countries, public health representatives may have limited experience managing such outbreaks (18).

This outbreak was difficult to identify due to the span of multiple years between cases. While the first clinical case was reported in 2018, the outbreak remained undetected until local public health nurses noted a common exposure between the two cases reported in 2021. Although WGS is routinely performed for *Salmonella* isolates in Ontario, the genomic linkage between cases was not flagged by the laboratory at the time due to the 60-day limit for initial PulseNet Canada cluster assignments. This illustrates the need to monitor and investigate any typhoid fever case for potential spatiotemporal and epidemiological linkages and to involve laboratory partners in surveillance and outbreak investigations to expand investigational options where relevant. It also highlights the potential benefit of expanding the PulseNet Canada relatedness analysis window beyond 60 days for *S.* Typhi, as recommended in another study examining typhoid fever outbreaks in the United States from 1999 to 2010 (17).

During this outbreak investigation, multiple factors limited the information available to generate source hypotheses, including the protracted length of time between cases, the varying modes of infection acquisition and the small number of cases. A case-control approach would have been problematic as responses to questionnaires are greatly affected by recall bias. Once we employed a multi-prong approach including WGS, social network analysis, a single interviewer and asymptomatic contact screening, we were successful in tracing cases to the primary source. Other outbreak reports have also highlighted the importance of using multiple methods in typhoid fever investigation (19,20).

The precarious nature of food handling work also hindered the investigation. The initial public health inspection of the implicated ready-to-eat counter failed to identify the carrier as an employee due to employment across multiple locations of the grocery store chain. In typhoid fever investigations, given the potential long period of exposure and transient food handler workforce, we recommend taking an extensive employment history of past, present and temporary food handlers. The exclusion from work for typhoid fever treatment and clearance also caused financial hardship to the food handlers. The negative impacts of excluding infected persons from work duties is likely to be shared within social networks, thus discouraging further cases and contacts from being interviewed and tested. Recent full compensation for those on medically mandated leave, such as that made available due to COVID-19 illness, presents a potential mechanism to facilitate employment insurance for other notifiable infections requiring exclusion from work (21).

Although there was no known direct contact, shared bathrooms or shared meals between case A (carrier) and case C (neighbour), we hypothesize that transmission potentially occurred through fomite contamination of common surfaces, such as doorknobs, railings or elevators. Likewise, although case H (the janitor) did not have known direct contact with case A or eat meals at the ready-to-eat counter, we hypothesize that acquisition likely occurred via common surfaces used by case A (carrier) at the grocery store (e.g., bathrooms). Training on hand hygiene and provision of proper personal protective equipment for janitors is essential to decrease the risk of enteric disease acquisition, as outside of healthcare and laboratory settings, janitorial work should not constitute an occupational hazard for infectious diseases (22).

Although outbreaks of typhoid fever are rare in Canada, they remain a risk particularly with international travel and immigration from regions where typhoid fever remains endemic (20,23). In addition, the emergence of drug-resistant *S.* Typhi in South Asia, increasingly observed in cases diagnosed in Ontario, has made effective treatment more challenging and prevention more urgent (8,24). The United States has reported cases of drug-resistant *S.* Typhi among individuals with no history of recent international travel (25). Surveillance and thorough case follow-up are essential to detect and control future outbreaks of typhoid fever (19,24).

Conclusion

This outbreak report describes a rare outbreak of typhoid fever associated with chronic *S.* Typhi carriage in Canada and contributes to the literature to inform future investigations. An interdisciplinary investigation was key to discovering the transmission source. This outbreak demonstrates the risk of infection and challenges in investigation among marginalized workers without comprehensive benefits or stable working conditions. The investigation also adds to the evidence for expanding the analysis window for *S.* Typhi WGS cluster assignment.

Authors' statement

JZ — Conceptualization, formal analysis & interpretation of data, writing–original draft, writing–review & editing
AJ — Conceptualization, formal analysis & interpretation of data, writing–original draft, writing–review & editing
TN — Investigation, interpretation of data, writing–review & editing
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JWalker — Investigation, interpretation of data, writing–review & editing
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Competing interests

None.

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